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Brain

A Journal of Neurology

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MARCH, 1937

BRAIN.

PART 1, VOL. 60.

CONDITIONED RESPONSES TO LIGHT IN MONKEYS AFTER REMOVAL OF THE OCCIPITAL LOBES.[1]

BY DONALD G. MARQUIS (YALE UNIVERSITY) AND ERNEST R. HILGARD (STANFORD UNIVERSITY).

SINCE the experiments of Munk (1890) and Brown and Schäfer (1888) it has been accepted that complete removal of both occipital lobes renders a monkey totally and permanently blind. Schäfer was able to demonstrate that the partial recovery of vision which had been observed by Luciani (1884), Ferrier and Yeo (1884), and Horsley and Schäfer (1887) was the result of an incomplete removal of the occipital lobes. Subsequent studies have shown that the essential cortical region is coextensive with the anatomical area striata (Poliak, 1932).

The tests of visual perception used in these studies were observational in nature. It was noted that, when moving about, the monkey bumped into walls and objects in its path. It was unable to locate food placed on the floor except by persistent exploration with its hands. It did not blink or make any other response to threatening gestures. The only reflex response which could be elicited by a bright light was pupillary constriction.

The question of a residual light sensitivity was raised, however, by Brown and Schäfer who wrote, in discussing the performance of a monkey after bilateral removal of the occipital lobes: "Although absolutely unable to see ordinary objects or to form any appreciation regarding them by aid of the visual sense, it is not quite easy to decide whether he is able to distinguish between light and darkness; for, when a large object, such as a tray, is held between him and the light, he will sometimes put up his hand as if to touch it. He does not, however, always respond in this way, and it is possible that the object may be appreciated by other senses than that of sight; for when a strong light is suddenly flashed upon him his attention is not diverted towards it" (1888, p. 316).

---

[1] From the Laboratories of Psychology, Physiology, and Neuroanatomy, Yale University.

The conditioned reflex technique offers a method by which any residual light sensitivity can be examined quantitatively. In the present experiments visual conditioned responses have been studied in a series of monkeys before and after bilateral removal of the occipital lobes.

METHODS.

Of the six monkeys used in these experiments, five were rhesus monkeys (*Macaca mulatta*) and one (OP 3) was a spider monkey (*Ateles ater*). Because the procedures were so nearly identical for all animals, individual protocols are not presented.

The operations were performed with full asepsis under deep general anæsthesia induced by sodium amytal. The occipital lobes were removed in two stages, with an interval of two to four weeks elapsing between the two operations. Since the primary purpose was to remove the area striata completely, radical extirpation of the entire occipital lobe was carried out. A large unilateral bone flap was turned down to expose almost the entire hemisphere. After the veins from the occipital cortex had been coagulated with the Davis-Bovie electrosurgical unit, the pia over the simian sulcus was gently incised with the cutting current. The sulcus was dissected to its depth with a blunt spatula and the ablation continued by gentle dissection with the spatula. On the medial surface of the hemisphere the line of transection was extended forward to the splenium of the corpus callosum, the lateral ventricle being opened at about the junction of the temporal and occipital horns. The occipital lobe was thus removed in one block, on which it was possible to identify the entire extent of the calcarine fissure.

Nothing in addition to the routine post-operative care of the animals was found necessary, for even after the second operation they would feed themselves adequately if food was left in the cage. A slight transient hemiparesis was noted after a few of the operations, but no permanent symptoms, other than visual, were observed.

The animals were studied for periods of seven to eighteen months following operation. At the conclusion of each experiment the animal was killed with ether and the brain fixed in situ by perfusion with neutral formalin. After hardening the brain was removed, weighed, and photographed, and the extent of the operative removal determined macroscopically. Sections through the margin of the lesion were stained with thionin for cytoarchitectonic study. Serial sections through the lateral geniculate body were prepared from two of the brains and stained with thionin for cell study.

The technique of conditioning used in this investigation has been described in detail in previous papers (Hilgard and Marquis, 1935, 1936). Conditioned eyelid closing to the noiseless exposure of a light was established on the basis of the unconditioned corneal reflex elicited by a brisk puff of air delivered automatically to one eye. The movements of the lids were recorded with the Dodge pendulum photochronograph. Artificial paper eyelashes, glued to the margin of the upper lid, projected into the beam of a Pointolite lamp, and the shadows were registered on film carried by the pendulum past a vertical camera slit. Specimen records are presented in fig. 3. Before training, there were no reflex responses to the light stimulus except an occasional lid opening. The interval between the exposure of the light and the succeeding air-puff was 400 ms., and the conditioned response appeared, after suitable training, as a lid closure following the light at a latency of approximately 200 ms. A daily conditioning session consisted of fifty paired stimulations, preceded and followed by a 5-trial series with a conditioned light stimulus only. Control records in which the monkey's eyes were shielded from the stimulating light showed no evidence at any time that the conditioned response was being elicited by secondary non-visual cues.

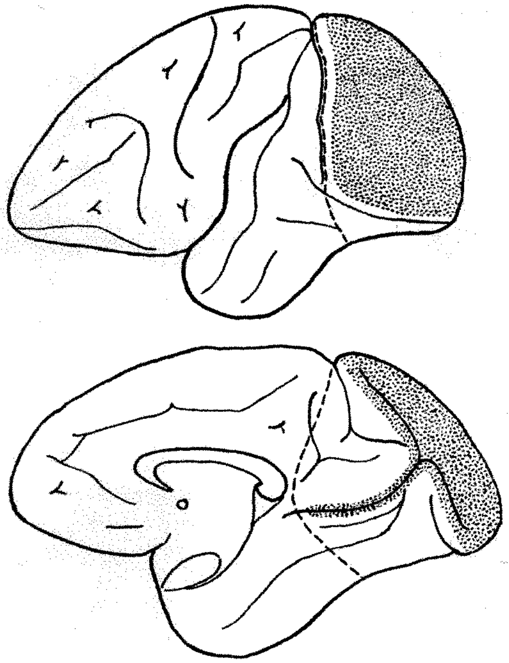

FIG. 1.—Lateral and medial aspects of the cerebrum of the monkey. The extent of the area striata according to Brodmann (1909) is shown by the stippling. The broken line indicates the line of the transection made in the removal of the occipital lobe.

RESULTS.

In all the animals the extirpation of the occipital lobes was found to have removed the area striata completely. In fig. 1 the extent of the extirpation is shown diagrammatically, and in fig. 2 the post-mortem photographs of the hemispheres of one of the animals are presented.

In no instance was any cortex of the striate type found in sections through the margin of the lesion. Further confirmation of the completeness of the removal was obtained in the two animals from whose brains serial sections through the lateral geniculate body were prepared. All the cells of this nucleus were degenerated, as has been described by Poliak (1932).

Following extirpation of one occipital lobe, the monkey showed a homonymous hemianopia. The threat reflex (blinking) was absent to stimuli in the contralateral half-fields, and in running about a room the monkey bumped against objects only on its blind side. The line of division between the seeing and blind fields appeared to pass through the fixation point. When the monkey was suitably restrained and induced to fixate its gaze upon a piece of food held directly in front of its eyes, it would not reach for a second piece of food moved from the blind to the seeing fields until the food crossed a vertical line through the fixation point. Such tests, however, could not be sufficiently accurate to permit a decision as to the presence or absence of macular sparing.

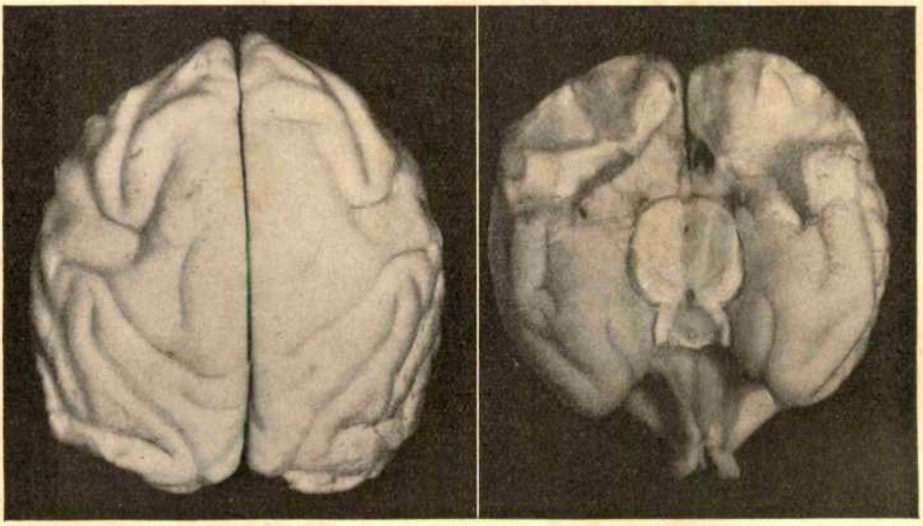

FIG. 2.—Photographs of the hemispheres of OP 5. The ventral-posterior view shows the opened lateral ventricle which was in free communication with the occipital cavity.

After bilateral extirpation of the occipital lobes, the monkey seemed completely blind, and our observations did not differ in any respect from those of Brown and Schäfer (1888). The threat reflex was permanently abolished, and no evidence of object vision was ever seen in any of the

PLATE I.

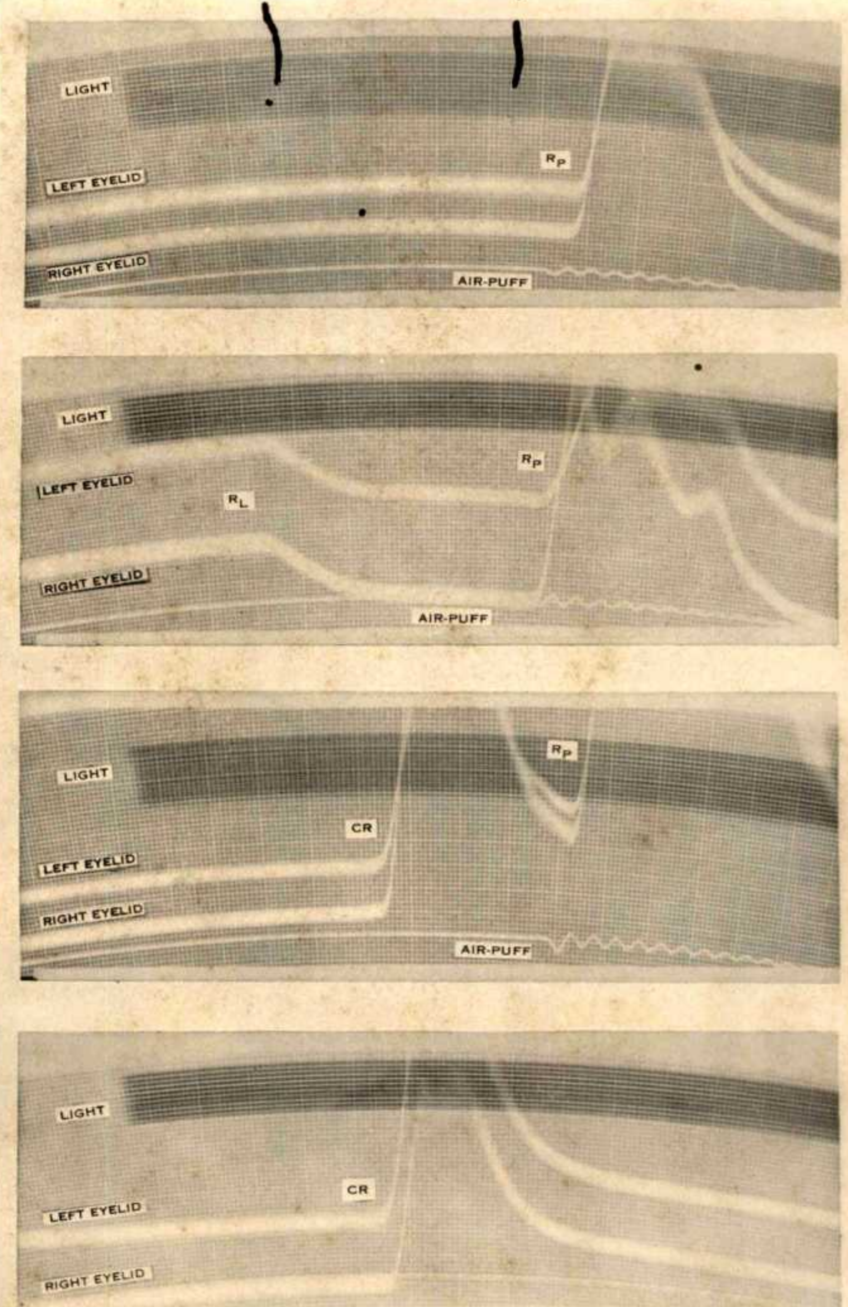

FIG. 3.— Specimen records of the process of conditioning (OP 5). The exposure of the light stimulus is recorded as a darkening at the top of the record. The unconditioned stimulus (air-puff) is recorded as a break in the lower line. Upward movement of the eyelid shadow corresponds to lid closure. Vertical time lines, 5 ms., emphasized lines, 50 ms. Record 1 illustrates the reflex (R_P) to the air-puff before conditioning. Record 2 shows the lid-opening reflex (R_L) which was present in about 20 per cent. of the trials before conditioning. Records 3 and 4 illustrate the conditioned response (CR) with and without reinforcement by the air-puff.

To illustrate paper by Donald G. Marquis and Ernest R. Hilgard.

animals. Some weeks after operation it was noted that the monkey would sometimes turn its head toward, or reach for, an object moved in the periphery of its visual field. A shadow seemed much more effective as a stimulus for this reaction than a bright light. The response, however, was so inconstant, and the difficulties of eliminating all sounds connected with the movement so great, that we were not willing to place any reliance on the observation.

The pupillary light reflex was not significantly affected. Following each operation, the pupils were equal and of normal size. The constriction to light was always present, but was restricted in magnitude for a period of one to three days following operation. Eye movements were normal with the exception of one animal (OP 11), who showed a paralysis of left lateral gaze for six days, following extirpation of the right occipital lobe. No reliable convergence or head and eye turning responses could be elicited by light stimuli.

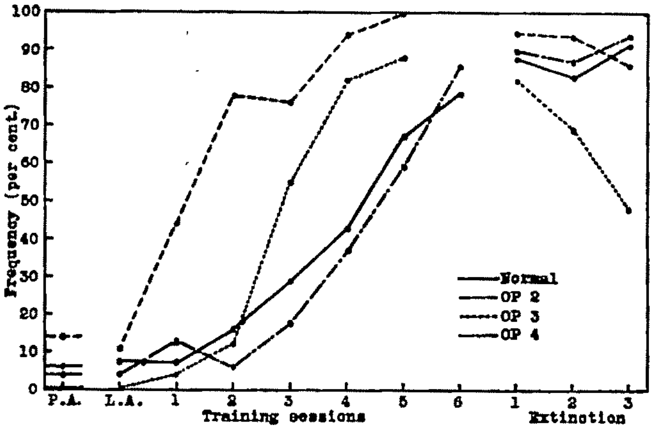

FIG. 4.—Course of acquisition of the conditioned response by three monkeys after removal of the occipital lobes, compared with the average of four unoperated monkeys. The frequency of response is plotted for the puff adaptation day (P.A.) as a control indicating the number of spontaneous responses resembling conditioned responses when no special stimulus has been presented. The light adaptation day (L.A.) yields a measure of the responses to the flash of light before conditioning. The final three days after the training sessions are retention tests without the air-puff. The expected extinction of the conditioned response when the reinforcement was omitted did not occur.

The only reflex eyelid response to the light stimulus used in the conditioning experiments was an occasional lid opening (fig. 3, record 2), although a much more intense light sometimes produced lid closure. The reflex opening was present at a latency of 100 to 170 ms. on about one-fifth of the trials in five of the six normal animals examined. After removal of the occipital lobes only one animal (OP 3, spider monkey) ever showed the reflex opening.

Acquisition of conditioned responses after operation.—The results of the conditioning experiments stand in clear contrast to the seemingly complete object blindness of the monkey after removal of both occipital lobes. Conditioned responses to light were established in three monkeys after bilateral operation. Their characteristics may be directly compared with conditioned responses of four unoperated normal monkeys, described in a previous paper (Hilgard and Marquis, 1936). With the exception of a slight increase in the latency of the response no difference could be detected. The conditioned response was qualitatively identical with the normal, appearing as a brisk, complete, bilaterally equal lid closing (fig. 3). Its course of development, measured in terms of frequency of appearance during each training session, showed no deviations from the normal greater than are encountered from one normal animal to another (fig. 4). The only reliable difference found between the two sets of observations was the increased latency of the conditioned response. The mean latency for the normal animals was 196 ms., for the three animals trained post-operatively, 230 ms. (Table I).

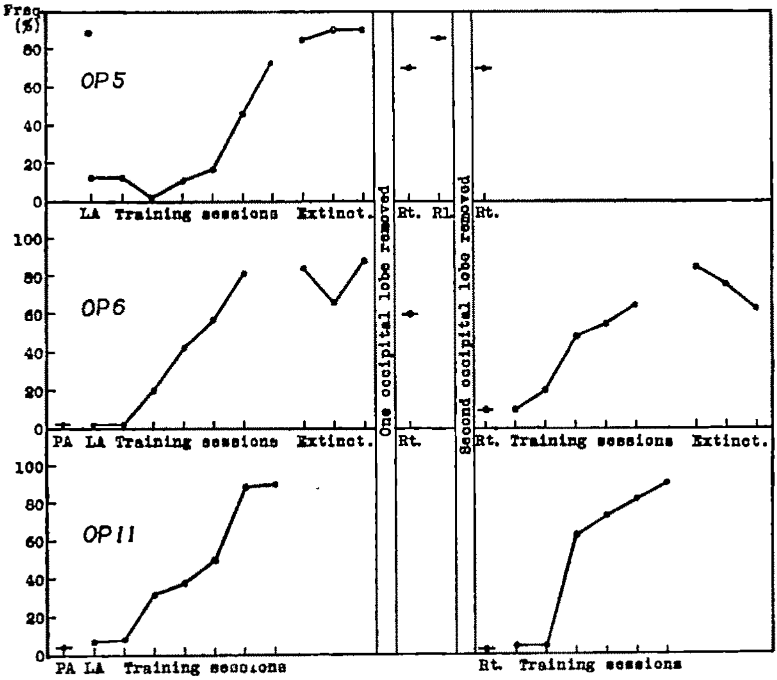

FIG. 5.—Course of acquisition and post-operative retention of the conditioned response in three monkeys. Rt. = retention test; Rl. = relearning session.

Retention of conditioned responses after operation.—The great similarity of the conditioned responses in the normal and in the operated monkeys is strong presumptive evidence that the neural mechanism of the response is the same in both cases, and that after removal of the occipital lobes the conditioned response is not mediated by a different mechanism functioning vicariously for the visual cortex. More conclusive evidence for this point would be furnished by the demonstration that conditioned responses established prior to operation were retained without further training after bilateral removal of the occipital lobes. This experiment has been attempted in three monkeys with somewhat inconsistent results. Since the procedures varied slightly for the different animals they will be described separately. The course of the pre-operative and post-operative training is presented in fig. 5.

In the first experiment (OP 5) there was perfect retention of the conditioned response. Before operation the response was brought to a stable frequency of 90 per cent. in nine experimental sessions. On the day following the extirpation of the left occipital lobe, the conditioned response was present and normal (no reinforcements with the air-puff are given in retention tests). Before the second operation there was a retraining session of fifty reinforcements, and retention tests on the day following removal of the right occipital lobe showed the conditioned response to be present at the slightly reduced frequency of 70 per cent.

The second experiment (OP 6) was carried out without any training between the two stages of the operation. On retention tests following the removal of the left occipital lobe, the conditioned response was present on 60 per cent. of the trials. Following the second operation, however, no conditioned response could be elicited. Retraining was instituted and the record of the development of the conditioned response presented in fig. 5 is practically indistinguishable from the pre-operative development, indicating what must have been a complete obliteration of the effects of the original training. This cannot be explained as ordinary forgetting with lapse of time, for in seven animals in which retention was tested over a rest period of three weeks, the frequency of the conditioned response decreased less than 20 per cent.

In the third experiment (OP 11) no training and no retention tests were given between operations. Following the removal of the second occipital lobe the conditioned response was absent, and redeveloped rather suddenly only after several sessions of retraining.

The present experiments do not, therefore, permit any clear interpretation of the data on retention of conditioned responses after removal of the occipital lobes. It is suggested by the observations on OP 5 that the inter-operative training session was effective in preventing the loss of the response, although it is not clear how this is accomplished. The training consisted of only fifty trials, many fewer than were necessary for learning or for relearning in other animals. The conditioned response was present at the beginning of the session, as it was in the case of OP 6, which was also tested after unilateral operation. It might be conjectured that some modification occurred in the subcortical centres of the operated side during retraining which made retention possible after the second striate area was removed, but further experimental analysis is obviously necessary for the understanding of the loss and recovery of habits after cerebral injury.

Since retention has been demonstrated in one case to be possible, these results are interpreted as confirmation of the previous inference, based on the similarity of the normal and post-operative conditioned responses, that the visual cortex is not the essential neural mechanism for conditioning to light stimuli. The failure of retention in the other two instances must then be ascribed to some sort of shock (diaschisis) effect upon other (presumably subcortical) optic centres. Similar abolition of the effects of pre-operative training with subsequent relearning has been observed in studies of the effect of removal of the occipital lobes upon the brightness discrimination habit in rats (Lashley, 1920) and dogs (Marquis, 1934).

The greater latency of the conditioned response noted in the animals trained post-operatively was equally apparent in the retention experiments. The latter data have a greater reliability because the observations are made on the same animal before and after operation and the differences cannot be ascribed to individual variation among animals. The mean latency of the conditioned response for each animal is presented in Table I.

TABLE I.—MEAN LATENCY OF THE CONDITIONED RESPONSE BEFORE AND AFTER REMOVAL OF THE OCCIPITAL LOBES (COMPUTED FROM ALL EXPERIMENTAL SESSIONS IN WHICH THE CONDITIONED RESPONSE EXCEEDED A FREQUENCY OF 75 PER CENT.).

Monkey	Normal	Operated
OP 9	153 ms.	
OP 5	215 ,,	240 ms.
OP 6	196 ,,	238 ,,
OP 11	221 ,,	274 ,,
OP 2		216 ,,
OP 3		252 ,,
OP 4		222 ,,
Average	196 ms.	240 ms.

During the course of development of the conditioned response the latency decreased as the frequency of response increased. This was true of the operated animals as well as the normal animals, but the average latency never reached the normal value. From fig. 6, in which the relationship between the latency and the frequency of the conditioned response is shown graphically, it is apparent that the differential between the normal and operated animals remained nearly constant throughout the course of the conditioning.

DISCUSSION.

The experiments reported here were undertaken to aid in the interpretation of the effects of destruction of the visual cortex in man and in other animals. The extensive utilization of animals for the experimental study of the functions of the cerebral cortex has unfortunately not been accompanied by any satisfactory basis for the application of the findings to man. When agreement between animal and clinical results is found no question is raised, but in many instances the observations cannot by their very nature be repeated on human subjects, and it is necessary to fall back on the assumption that the more similar the two species the more likely are the findings applicable to both.

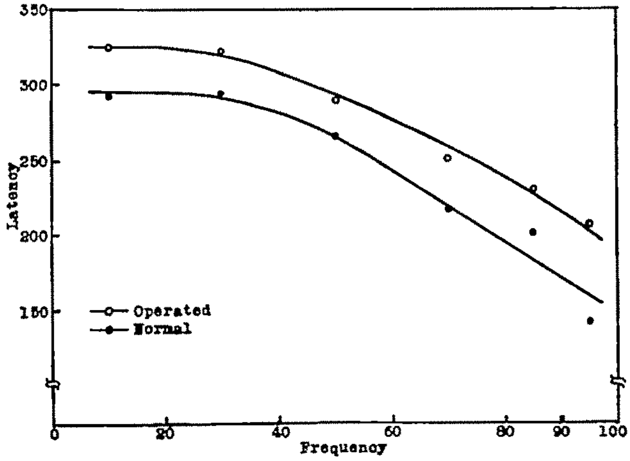

FIG. 6.—Decreasing latency of the conditioned response during its development in four normal and six operated monkeys. Each point represents the mean latency of all responses occurring on days in which the percentage frequency of response fell within the limits indicated on the abscissa.

There is one guide which has proved serviceable in understanding the differences in cerebral function between different animals: the principle of encephalization, which states that in the phyletic series there is a progressive shifting of functions from lower neural levels to higher. Derived principally from comparative anatomical studies, it has been amply verified by the results of experiments on the cerebral motor area. This principle gives an indication of the direction of the difference between animals, but in its present formulation it offers no clue to the magnitude of the difference.

The principal stages in the encephalization of visual function have been outlined elsewhere (Marquis, 1934). In the lower vertebrates (fishes, amphibia) the visual correlation centre is the optic tectum of the mesencephalon. In mammals there is in addition a cortical visual centre with a projection from the lateral geniculate body. Within the mammalian series there is a progressive increase in the size, structural differentiation, and functional importance of the geniculo-cortical system at the expense of the mesencephalic centres.

Removal of the cortical visual centre in rabbits or rats abolishes the discrimination of visual form and pattern, but the animals can respond to the brightness and position of a stimulus object. Dogs are also able to discriminate light intensity after removal of the occipital lobes, but give no evidence of distinguishing position and distance. Clinical observations show that destruction of the area striata in man produces a complete blindness in which even the perception of light and dark is abolished. This significant difference between the dog and man made it desirable to investigate an intermediate species.

Directly comparable data are available for the dog and monkey with respect to visual conditioned responses. In both animals the conditioned response, after bilateral removal of the area striata is virtually unaffected. It can be established at the same rate as in normal animals, and has the same general characteristics with the exception of a slight increase in latency. In this respect, therefore, the monkey is more similar to the dog than to man, and there remains a large qualitative change in cerebral visual function between the monkey and man.

In one respect the effect of removal of the occipital lobes was more severe in the monkey than in the dog. In the latter, perfect retention of a conditioned response established prior to operation was observed in every case. Of three monkeys, only one retained the conditioned response after operation, although the other two reacquired the response with retraining.

The cerebral localization of those visual functions which remain after removal of the occipital lobes is a problem which cannot be finally answered with the present evidence. There are several reasons, however, for believing that the conditioned responses are mediated by subcortical mechanisms rather than by extra-occipital cortical areas. Anatomical studies (Poliak, 1932) have shown that in the monkey the optic radiation terminates exclusively in the area striata, so that the only pathway of entrance to the cortex for visual impulses must necessarily have been destroyed by the removal of the occipital lobes. Furthermore, it has been shown in lower mammals (dog, rabbit) that certain visual functions persist after complete removal of the cortex, and must necessarily be subcortical. A critical test of this has not been possible in monkeys because an adequate period of survival after bilateral removal of the cerebral hemispheres has not been obtained. Visual function cannot be satisfactorily tested in the hemianopic fields following removal of one hemisphere because of the diffusion of the stimulating light to the seeing fields.

SUMMARY.

After bilateral removal of the occipital lobes, including all of the area striata, the monkey behaves as though it were totally blind. When moving about it bumps into walls and objects, it pays no attention to food placed or moved before its eyes, and it does not blink or respond in any way to threatening gestures.

A conditioned response to a light stimulus was established in three monkeys after removal of the occipital lobes. The rate of formation of the response, as well as its form, amplitude, and frequency, were not significantly different from the normal. The only difference detected was a slight increase in latency.

In three monkeys, the conditioned response was established before removal of the occipital lobes. One monkey retained the response after operation; the other two reacquired the response with retraining.

The similarity of the conditioned responses in normal and operated monkeys provides evidence that the visual cortex is not an essential part of the neural mechanism for responses to light stimuli. This is further supported by the demonstrated possibility of retention of a conditioned response established prior to operation. While the visual cortex is necessary for all object vision depending on the spatial characteristics of the stimulation, the only discovered effect of its removal on responses to light is a slightly increased latency and an obliteration in some instances of the effect of previous training.

Comparison of the effects of destruction of the area striata in rodents, dogs, monkeys, and man reveals a progressive encephalization of visual function in the mammalian series, with the greatest qualitative difference occurring between monkey and man. These results suggest that great caution is necessary in interpreting human cerebral function on the basis of animal experiments.

The authors desire to express their appreciation to Professor J. F. Fulton who performed the operations, and to Professor H. S. Burr for valuable aid in the anatomical studies. Part of the expenses of the research were defrayed by a grant from the Research Fund, Yale University School of Medicine.

REFERENCES.

Brodmann, K. "Vergleichende Lokalisationslehre der Grosshirnrinde." Leipzig. 1909.

Brown, Sanger, and Schafer, E. A. "An Investigation into the Functions of the Occipital and Temporal Lobes of the Monkey's Brain," *Phil. Trans. Roy. Soc Lond.*, 1888, **179B**, 303-327.

Ferrier, D., and Yeo, G. F. "A Record of Experiments on the Effects of Lesion of Different Regions of the Cerebral Hemispheres," *ibid.*, 1884, **175**, 479-564.

Hilgard, E. R., and Marquis, D. G. "Acquisition, Extinction, and Retention of Conditioned Lid Responses to Light in Dogs," *Journ. Comp. Psychol.*, 1935, **19**, 29-58.

Idem. "Conditioned Eyelid Responses in Monkeys, with a Comparison of Dog, Monkey, and Man," *Psychol. Monog.*, 1936, **47**, 186-198.

Horsley, V., and Schäfer, E. A. "A Record of Experiments upon the Functions of the Cerebral Cortex," *Phil. Trans. Roy. Soc. Lond.*, 1888, **179B**, 1-45.

Lashley, K. S. "Studies of the Cerebral Function in Learning," *Psychobiol.*, 1920, **2**, 55-135.

Luciani, L. "On the Sensorial Localizations in the Cortex Cerebri," *Brain*, 1884, **7**, 145-160.

Marquis, D. G. "Effects of Removal of the Visual Cortex in Mammals, with Observations on the Retention of Light Discrimination in Dogs," *Proc. Assoc. Res. Nerv. Ment. Dis*, 1934, **13**, 558-592.

Marquis, D. G., and Hilgard, E. R. "Conditioned Lid Responses to Light in Dogs after Removal of the Visual Cortex," *Journ. Comp. Psychol.*, 1936, **22**, 157-178.

Munk, H. "Ueber die Functionen der Grosshirnrinde," 1890. Berlin.

Poliak, S. "The Main Afferent Fibre Systems of the Cerebral Cortex in Primates." Berkeley: Univ. Calif. Press. 1932.

MUSICOGENIC EPILEPSY.

BY MACDONALD CRITCHLEY.

THE aim of this paper is to describe the occurrence of epileptiform attacks in factual association with the hearing of music.

A previous communication dealing with reflex epilepsy [1, 2] indicated that there existed cases in which auditory stimuli were capable of evoking a seizure. Whilst the majority of such cases of "acousticomotor epilepsy" were precipitated by sudden and unexpected noise, there was a small but well-defined group in which musical sounds alone were effective. Two or three illustrative cases were cited.

Opportunity has since brought to notice a series of such cases of "musicogenic epilepsy" (or "musicolepsia"), while a close scrutiny of neurological literature has added only a few additional examples.

Cases of this phenomena are too rare to permit dogmatic conclusions as to the clinical features which may be regarded as characteristic. From such evidence as is available, however, it appears that the association between stimulus and attack is a close one; only rarely does a seizure occur without the precipitating factor of music. On the other hand, music may be heard without an epileptic attack necessarily following. There is reason to believe that in some cases only certain types of music may be followed by unconsciousness. An attack does not usually follow promptly the onset of the music, and the stimulus may need to be maintained for many minutes before producing a fit. The character of the epileptic phenomena proper varies from transient "absences" or obfuscations of consciousness, to complete major attacks with convulsive movements and vesical incontinence.

PERSONAL CASES.

Case 1.—F. C., female, aged 25, consulted me in the out-patient department of the National Hospital in 1931. Since the age of 17 she had been subject to attacks of "faintness" on hearing certain types of music—particularly that produced by piano or organ. She fancied that "classical" music was more noxious than dance music, though she was not sure upon this point as she had little or no musical knowledge. She was unable to resist the attacks and was obliged to lie down on the floor. Immediately before an attack she suffered a sense of "weakness" and pins and needles in the legs, spreading thence to the rest of the body. The feeling was a horrid one ". . . as if the nerves were all on edge." Then voices would become distant and she would remember nothing more. Once only had she micturated during an attack and bitten her tongue. On recovery she would feel very sick and usually "had a good cry." She had had as many as four attacks a day. Her previous health had been good and the family history unimportant.

Examination revealed no definite physical abnormality.

On her admission to hospital, gramophone records were played, with her consent, so that a personal observation could be made of the effects of music. At first a dance tune was tried, but she soon remarked that such music would not produce the desired effect. An orchestral record was then chosen ("Valse des Fleurs," from Tchaikowsky's Casse-Noisette Suite, played by the Berlin State Opera Orchestra). After about fifteen seconds her face took on a restless and pained expression, and the respiration became laboured. The eyelids opened and shut rapidly, and then began to flutter. She appeared distressed, her fingers clutching the bed clothes, and her lips performing rapid "smacking" movements as if she were tasting something unpleasant. Then a fixed and vacant expression became noticeable, followed at once by generalized clonic convulsions. Movements of the face were especially marked, and there was considerable frothing. The face was flushed and cyanotic; the head was deviated to the left side, the eyes being turned upwards and to the left.

At the onset of the fit the plantar responses were unobtainable; two minutes later there was a left-sided Babinski reflex, shortly afterwards both plantar responses were extensor in type. The knee-jerks were absent though the ankle-jerks were present.

Three minutes after the cessation of convulsive movements the patient opened her eyes, but seemed still oblivious of her surroundings and did not reply to questions. She rolled her head slowly from side to side.

Half an hour afterwards she was able to discuss her attack . . . "as soon as the second record started, my inside seemed to turn right over. My arms and legs went cold and numb from below upwards. I screwed up my eyes and mouth because I didn't like it. I tried to fight against it. I had no nasty taste, smell or any other uncomfortable feeling (in reply to direct questioning.) The numb feelings got stronger—then I went as if I were dead—I could no longer hear anything—and then I lost consciousness. When I came round I was alone. I've now got a vile headache."

She was kept under observation as an out-patient. Despite treatment with bromides and luminal, she continued to be afflicted with similar attacks, almost every one of which was precipitated by music.

Case 2.—L. P., female, aged 46, attended the out-patient department of the National Hospital, Queen Square, on account of occasional epileptic attacks of four years standing. Her previous health had been good. No abnormal physical signs could be found on examination. When questioned as to the circumstances preceding her attacks she revealed that they would occur when listening to music, or if she became deeply interested in a conversation. The music had to be "reminiscent" in type. Old-time songs, especially if sad, were particularly provocative; dance-times did not affect her however. If she heard sentimental music being played she would not dare listen, but had to hurry out of earshot.

Case 3.—A. B., female, aged 51, consulted me on September 12, 1934, complaining of attacks of unconsciousness and also of "day-dreaming" of seven years' standing. She stated that she was quite well until one evening while listening to the music of a Radio dance-band she suddenly fell back unconscious. A month later another similar attack occurred, again while listening to the wireless. On another occasion while attending an organ recital she suddenly lost consciousness and on recovery, felt an intense headache. Thereafter she avoided as far as was possible listening to any solo music. She also became liable to attacks of "day-dreaming" which would come on in a cinema or any other place where music was being played, especially if the tune possessed a well-defined rhythm. On one occasion, a "day-dream" occurred during a patter-dance, and once also at a lecture where the speaker had an unusually monotonous and sing-song diction. She cannot describe her day-dreams, but speaks of them as nightmares in which she feels "horribly frightened," and also as if "she had been through it all before." They are momentary and, as far as she can tell, are unattended by unconsciousness. Two months ago, she had an attack of unconsciousness with convulsion and incontinence, not however preceded by music.

The family and previous histories were uneventful.

She was admitted to the National Hospital, Queen Square, where no physical abnormality could be detected. Lumbar puncture revealed a normal fluid under a pressure of 110 mm. of water.

During her stay in hospital two tests with gramophone music were carried out, on each occasion with the production of abnormal phenomena. Thus on September 27, 1934, during the playing of a rather loud fox-trot with a well-defined tempo she suddenly became pale and slightly cyanosed. She leant forward in her chair with a frightened look in her eyes (which watered a little) and she began smacking her lips. Her pulse-rate had risen to 120 beats per minute. The plantar responses were flexor but two minutes later they were both distinctly extensor in character. At this point the examiner pricked her with a pin. After about forty-five seconds she blinked her eyes and looked about her.

Questioned as to what had happened she replied "that was one of my day-dreams—like a nightmare—it was as if I had been through it all before. I was frightened of something but I cannot say what that something was." She denied any subjective alteration in vision or sensation, but she did not remember being pricked with a pin, or having her plantar reflexes tested.

The patient still continues to attend the out-patient department and still suffers from both kinds of attack (unconscious spells and day-dreams) on hearing music.

Case 4.—G. W., female, aged 33, attended the neurological out-patient department at King's College Hospital on September 21, 1934, suffering from epilepsy for the past three years.

The first attack occurred while alone in the house, listening to the wireless. She suddenly "felt funny" she could not "get her voice," everything "went black and further and further away." She felt very frightened, ran upstairs and fell unconscious at the top. She frothed at the lips but there was no biting of the tongue or involuntary micturition. A week later a similar attack occurred, again while listening to the wireless. She was then put on treatment with luminal, but one or two similar turns appeared at rare intervals, each one being precipitated by hearing music. All except one or two of her turns have occurred at the time of her periods and she has never had an attack independently of music. In one attack she bit her tongue. Her husband says that a turn starts by the patient being very frightened and she screams with terror; her face then screws up to one side and becomes distorted; one leg draws up and she then stiffens and would fall if he did not catch her. The face becomes bluish and there is a little froth at the lips. The duration is described as a matter of seconds. Afterwards she is rather dazed for half an hour.

There was nothing noteworthy in the family history or in her previous health.

Physical examination revealed no abnormality. She was however markedly nervous and apprehensive, and worried about her malady.

She was admitted to the National Hospital, Queen Square, in October, 1934, where an attempt was made to precipitate an attack by means of music.

After various records had been played for about fifteen to twenty minutes a waltz record of Strauss's "A thousand and one nights" was followed by signs of distinct uneasiness. The record was replayed and she became rather more disturbed. She put her hands over her ears, screwed up her eyes, frowned, and made numerous other nervous grimacings. She registered obvious relief when the record came to an end. When questioned she said she did not like the music, that it "sort of jarred" terribly and that if she had been at home she would have taken off the record. The sensation was not like that of the fear which usually heralded her attacks.

The patient still attends my out-patient department and at times sustains attacks after listening to music. This especially occurs at the time of her periods. Any kind of music may precipitate an attack, but especially "classical pieces, waltzes, and nice songs." She is very fond of music and possesses more than average musical taste and education.

In addition to the foregoing four cases, I have been permitted to quote the following cases by the kindness of Professor Sir Arthur J. Hall, the late Professor L. Bouman, Dr. C. P. Symonds and Dr. Fergus R. Ferguson.

Case 5.—Male, aged 22, had suffered from occasional attacks of epilepsy for some years. He was an accomplished pianist, and to his regret he found that the attacks occurred always while playing the piano. It is not certain whether attacks also occurred at other times.

Case 6.—A., male, aged 26, began to suffer from epileptic attacks four years previously. Every fit except one was associated with his playing the piano. In one attack he bit his tongue, but involuntary micturition had never occurred. He was kept under observation by Professor Bouman for the next seventeen years. Later, fits also occurred independently of music, but he continued to have attacks, as, for example, when his brother played the 'cello. Despite transitory psychoneurotic episodes, he was able to carry out his duties as the manager of an important factory with complete satisfaction.

Case 7.—V., male, had his first epileptic fit at the age of 32, after hearing a barrel-organ in the street. His second attack occurred while playing the piano. Two months later, his third attack occurred: after dinner at his parents' house, the family assembled to hear his brother play the piano. The patient quickly became uncomfortable, noticed a tinnitus, and as he was sinking into unconsciousness, was just able to call out "stop, please," before losing his senses altogether. A typical epileptic attack supervened. Other similar turns followed: once when at the opera "Lohengrin," and once again when a barrel-organ played outside his house.

The patient remained under treatment with regular small doses of bromide, and ultimately died at the age of 62, from an embolus after prostatectomy. His widow writes that her late husband suffered only three or four attacks during his married life. He largely lost his susceptibility towards music, and during his last ten years of life was able to attend concerts regularly.

Case 8.—Male, aged about 25; a wireless operator on a liner. Generalized epileptiform attacks of a minor character would occur whenever he heard a brass wind instrument play bass notes. On this account he had to transfer to smaller ships which carried no orchestra.

Case 9.—A woman who had previously been subject to migraine, sustained her first epileptic fit at the age of 25. There was a family history of migraine, epilepsy, and also of manic-depressive psychosis. Over the course of six years the patient sustained eight or nine attacks. She was a talented musician and owned a music-room. All but one of her attacks had taken place in the music-room either when she or someone else was playing the piano. The only exceptional case had occurred at a time when she was thinking out a tune "in her head." Some time later, whilst pregnant, the patient made a suicidal attempt.

Case 10.—Male, aged 40. During the War he was wounded in the right temporal region. At the age of 32 the first epileptic attack occurred. Since then, he has had about ten attacks. Two of his fits had occurred whilst listening to a concert. Another attack took place after he had been sawing for a period. The patient himself stated that when he is listening to the radio, and a certain note is sounded, he feels extremely uncertain of himself and as though he might be going to have an attack. It is noteworthy that each of his fits is preceded by an auditory aura of a rushing or swishing noise in the left ear.

Case 11.—Dr. C. J. C. Earl has also described to me an epileptic patient of his whose attacks were always ushered in by a complicated psychological aura. Each fit was precipitated by listening to pianoforte music.

Neurological literature contains only a few accounts of epileptic attacks being produced by musical sounds. A number of these records have been published only in obscure Russian periodicals and have largely escaped notice.

Probably the first communication is that of I. P. Merzheevsky in 1884 [3]. The patient had sustained three fits provoked by melodies and musical tones new to the patient. At a concert an unfamiliar tune would produce a constriction in the throat followed by pallor. If the patient were prevented from immediately leaving the hall an epileptic fit would supervene, with biting of the tongue. When the patient grew accustomed to a melody the fit did not occur. Sometimes, a new tune provoked only dizziness, something like an aura.

A few years later, Steinbrugge [4] observed a 45 years-old patient who had had epileptic fits from the age of 15, having convulsions every time he heard music, while all other sounds, however loud, were without such effect.

The next communication was that of Y. Y. Trutovsky [5]. His patient, a man of 31, in whom an attack of epilepsy, provoked by pianoforte music, was observed during his stay in hospital. Another of his patients suffered a type of "affect-epilepsy" together with episodic periods of confusion with hallucinosis. One variety of attack was usually precipitated by violent noise of some kind; in the hospital one such attack was witnessed being brought on by piano music.

In 1905, H. Oppenheim [6] mentioned briefly the case of a woman of 45, who was liable to two types of epileptiform attack: in the milder variety she would suddenly become anxious, and then utter a cry. The mouth then became pulled up to the right, and the right half of the body jerked; consciousness was not completely lost. In her severer attacks there was total unconsciousness and the tongue would be bitten. Such attacks corresponded closely with the time of menstruation and occurred mainly at night, or during an afternoon sleep. When they happened during the waking state, they were always associated with music.

The most important contribution however is to be found in an obscure paper by v. Bechterew [7], on "reflex epilepsy provoked by sound stimuli," published in 1914. Owing to the inaccessibility of the original paper, which is written in Russian, this work may be quoted in some detail. Bechterew mentions two cases, giving particulars of one. This patient was a well-known man of letters, Nikonov, who has fortunately put on record a detailed account of his own case in a manuscript, entitled, "Fear of Music." Bechterew, in his article, has reproduced this work verbatim, and excerpts may be given here: "Despite the fact that the unpleasant sensations (i.e. twitchings of the eye, palpitation, apprehension) began to recur more and more frequently—and invariably took place when I was at a musical performance alone, I bravely went to performances—I used to get disturbed by these incomprehensible twitchings of my eye and shocks in my throat to the point of perspiring all over and even trembling. However, the following incident inspired me with a real fear of music. I was present alone at a performance of "The Prophet," at the Imperial Opera Theatre in St. Petersburg. The first two acts passed without trouble. The ballet began, representing 'skating on ice—I felt rapid twitchings in my left eye. Then I experienced convulsions in my throat. I grew alarmed, stopped my ears, and with an effort closed my left eye, but the convulsion in my throat increased. And suddenly I felt I was losing consciousness. The twitching in my eye and the shocks in my throat, increasing, passed into a sensation of violent pain in the crown of my head, as if someone was hitting me there as hard as he could with a heavy object. Darkness enveloped me, and with the thought that the end had come, I lost consciousness. From that moment I began to experience a real fear of music—I was afraid of loud music near at hand. Then I found I had reason to fear distant and subdued music as well—eventually I found that at times even ordinary pianoforte music had the same effect on me even when played in a neighbouring flat, and I heard it through the wall. And once I experienced twitchings in my eye and shocks in my throat from the sounds of an accordion. The fear I experience when I hear music is sometimes accompanied by perspiration and palpitation of the heart. If in the street I happen to meet a military band, I display extreme cowardice, I run from it wherever I can into a side street, the gates of a neighbouring house, or to the first shop I see."

The writer proceeds to discuss what particular types of musical sound affect him most, and also to analyse the relationship of his emotional appreciation of music with the untoward subjective symptoms engendered.

Bechterew adds a note that fits recurred in this patient, each one being precipitated by music, but were ultimately cured by a course of bromide treatment.

In 1929 E. Redlich [8], writing on the psychogenesis of epilepsy, mentioned a patient in whom music, especially that of the violin, would produce a sensation of throttling going on to unconsciousness.

K. Goldstein, in 1931 [9], demonstrated a man, aged 32, who for five years had been liable to attacks lasting five to ten minutes, at first without disturbance, but later with loss of consciousness. He sometimes suffered as many as ten to twelve a day. In each attack a curious tonic state developed, with a fixed attitude and pupillary dilatation. The plantar response would be unobtainable. Each attack would be precipitated by music, and Goldstein was able to produce a tonic attack by playing a gramophone record. In the discussion which followed this communication, Bonhoeffer referred to a similar case in which epilepsy had started at the age of 30 during lactation. At first there was no precipitating factor demonstrable, but later, the fits became intimately associated with the hearing of music. The attacks were certainly epileptic in nature, and it was of interest that the patient's son was also an epileptic.

A recent paper by M. P. Nikitin [10] deals with a male, aged 30, who for seven years had been subject to nocturnal epileptic attacks. For five and a half years he became liable, during the day following a fit, to feelings like electricity passing from the right side of the chest to the head, and associated with transitory disturbance of consciousness. For three and a half years these latter sensations would take place whenever he sang a certain song, or heard someone play or sing this air, or even when he imagined the tune to himself. This had taken place on some thirty occasions. Whilst in hospital he was asked to sing this song (the aria of Zaren Berendej from Rimsky-Korsakow's "Snegurotschka"); he became cyanosed with the first few bars and then passed into a complete epileptic fit. On another occasion he was asked to sing this melody in order that a cinema film might be made, but he developed only a dreamy state, without convulsion. When singing this piece before the Leningrad Neuropathological Society, the patient sustained merely the aura in the right side.

CLINICAL FEATURES.

There are therefore about twenty instances of musicogenic epilepsy available for study, including the eleven personal cases. One or two points of clinical interest are noticeable. In the first place the age at which the epileptic phenomena make their first appearance has often been later than usual in the idiopathic varieties of epilepsy. Of 16 cases where the age of onset is known, 11 began at or after the age of 25 years. Males and females have been affected the proportion of 10 to 7; in three reports the sex was not given.

The patient's musical knowledge and appreciation may possibly be significant. My first patient could not readily distinguish dance from "classical" music, while my second was also uneducated in musical affairs. The third confessed that she was "fond of light music," though possessing very little knowledge of the subject, while the fourth was above the average in her appreciation of music. Case 5 was very fond of music and an accomplished pianist. My sixth patient described himself as very fond of music and very sensitive to the environment of the stage; he had been known to burst into tears during a performance of "Cyrano de Bergerac," and also while Sarah Bernhardt was acting. No. 7 is reported as "from childhood being always very sensitive to disharmony." The ninth was a talented executant who owned her own music-room. Goldstein's patient also appreciated music, while Bechterew's patient, "Nikonov," possessed an advanced æsthetic development and was a well-known professional critic of music.

Information as to the specific characters of the epileptogenous stimuli has not always been available. In the first case "classical" music was inculpated, whereas the second patient recognized "old-time" or "reminiscent" melodies as the most potent. My third patient stated that a well-punctuated rhythm was for her the most dangerous feature in music, and that on occasions a tap-dance or even a monotonous voice had proved effective. The fourth patient found that sentimental songs heard upon the radio were most apt to produce an attack. In this case and in the fifth, attacks might occur while the victim was playing the pianoforte. Deep notes from a brass wind instrument proved the only stimulus in the eighth case, and in the tenth case also, it seemed as though a particular note in the music proved operative. Merzheevsky specified that new and unfamiliar tunes were the only ones capable of evoking an attack. Redlich's patient was particularly susceptible to the violin. In the case reported by Nikitin, only one melody could provoke a fit, whether the patient sang this tune, or heard it played, or merely imagined it to himself. The patient Nikonov—described by Bechterew—was able to furnish the most detailed information. Here, continuous or comparatively protracted musical periods were disturbing;

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most noxious of all was the so-called "musical background" as adopted by Wagner, which afforded an unrelieved and inescapable sound-procession. Loud music proved more and more dangerous than quiet; wind instruments more than string—violins, however, made an exception, and Nikonov describes their persistent high-pitched tones as "excessively intolerable." Instrumental music was worse than vocal; while slow music was more endurable than quiet lively melodies and especially those with a distinct rhythm. Dance and march music was particularly unbearable and alarming.

The character of the epileptoid phenomena has varied in these cases, ranging from a mere aura to complete major attacks with convulsions, incontinence, and biting of the tongue. Between these extremes lie the minor "absences" accompanied by transient clouding of consciousness and smacking of the lips. In Cases 1 and 3, the plantar responses were observed to change during and after an attack, from flexor to extensor, passing through a stage of being unobtainable. Goldstein's patient showed attacks which were purely tonic in character. Nikitin's patient showed on different occasions epileptic phenomena of various degree of complexity as the result of the musical stimulus.

The emotional state between the hearing of the music and the beginning of the epileptic fit is a most important factor, especially in discussing pathogenesis. Our available information is rather scanty and it is at times difficult to disentangle the affect produced by the music from the psychical aura belonging to the attack. Unpleasant, disagreeable or frightened sensations immediately before the fit are described by the first, third and fourth patients. The first of these ascribes the fear, however, to the knowledge of the impending attack. My second patient referred to a feeling of sadness just before losing consciousness, but here the mood may possibly be related to the sentimental and old-fashioned type of musical stimulus, and to its attendant associations. Patient No. 7 described his aura as a feeling of being submerged in water; a sense of insecurity "as if the surroundings had vanished." Nikonov, in his autobiographical record, said that as a boy he would feel when he heard music something like a sudden blow, a very strange and frightening sensation. Certain physical symptoms would also appear, as already described, but these were transitory and not in themselves unpleasant, though alarming because of their novelty. Ever after the time when these sensations had culminated in unconsciousness, he began to develop a real fear of music. At the first hint of these premonitory symptoms he would hurriedly escape out of earshot.

In one case (No. 3) the preliminary sensations included elements other than those of fear. Something approximating to the *déjà vu* phenomenon may be read into the description. . . . "I have the feeling that I have been through it all before; as if I were going through a scene. It is the same scene on each occasion. People are there, dancing; I believe I am on a boat. The scene is not connected with any real place or event which I can recall."

An attack does not inevitably follow the onset of premonitory symptoms and some of the patients with musicogenic epilepsy develop the power of inhibiting an attack. Thus my third patient stated that if she were to hear the music without *listening* to it, no attack would follow. Nikonov, too, found that in the early days no aura would develop if he could divert his attention from the music from time to time. He was therefore more likely to experience epileptic phenomena if he went to the Opera alone. After the appearance of his first fit, he still believed that an attack was less likely to materialize if a strong emotional reaction accompanied the hearing of the music.

PATHOGENESIS.

Discussion of the means whereby a musical stimulus can provoke an epileptic attack is purely speculative in character. In the more common types of acusticomotor epilepsy, one usually imagines a response to the emotion of surprise or startle as the probable mechanism; obviously no such speculation can be applicable to the musicogenic cases. We seem rather to be dealing with an unusual and specific intolerance towards musical sounds, somewhat reminiscent in fact of the common dislike of music evinced by dogs. The analogy is strengthened by the occasional occurrence of convulsions in dogs as a climax of musically induced discomfort. Dr. Grainger Stewart has told me of a spaniel of his acquaintance which will fall convulsed when music is played nearby. Another such case has been described by Erlitzky [11], the dog later becoming mad; Billroth also narrates how he saw a young great dane fall unconscious when a village brass band struck up a Schutzenmarsch.

There is yet a third type of acusticomotor epilepsy which—very much rarer than the two other varieties—seems to occupy a kind of intermediate position. In this type, epilepsy is provoked by auditory stimuli of a monotonous character, and the factors of surprise as well as of musical quality do not enter. A case in point was that of E. M., a boy, aged 11 years, subject for eighteen months to minor epileptic attacks. Although many of the fits would occur spontaneously, the patient declared that an attack would always develop if he heard a noise of a continued and monotonous order, such as an aeroplane in flight, machinery in a workshop, a kettle on the boil or wireless talks. In this case music was without effect, as were abrupt unexpected sounds; in the boy's own words, the noise "has to keep on" before a fit developed.

Some neurologists have favoured a purely mechanical view of musicogenic epilepsy and have visualized a greatly increased vascularity of the cortex produced by music, as the precipitating factor. Such a view runs counter of course to a fairly widely diffused impression that a process of local ischæmia precedes the epileptic fit. As a matter of fact, Gibbs, Lennox and Gibbs [12] were unable to demonstrate any significant change in the cerebral circulation immediately preceding the onset of seizures.

Whether music actually does increase the cortical blood-supply is not established. The physiological effects of music have not been the subject of much serious study within recent years. What data is available (Dieserens [13]; Schoen [14]), appears to show that music can produce: (1) An increased bodily metabolism; (2) either an increase or a decrease in muscular energy; (3) an irregular and accelerated respiration-rate; (4) heightened acuity of other special senses; (5) an exaltation of the knee-jerk, directly proportional to the strength of the auditory stimulus; (6) a lowered threshold for various sensory stimuli; (7) a marked but variable effect upon blood-pressure and the peripheral and cerebral circulations.

The last-named is obviously the most significant effect in relation to musicogenic epilepsy. An old human experiment described by Patrizi is of interest here. A boy, aged 13, received a severe cranial wound from an axe. The boney gap 5 in. in length allowed the pulsations of the brain to be plainly visible. Plethysmographic records were made of the cerebral pulsations and it was clearly demonstrable that an increased cerebral circulation took place under the influence of music, the effects varying somewhat according to the intensity, characters and tempo of the melody, as well as according to the pitch of a single note.

Findings such as these obviously need verification before they can be accepted unreservedly. In any event, an increased cerebral vascularity after music, even if established beyond all doubt, leaves unexplained why we do not all become convulsed on hearing music. In the same way, even if a cerebral engorgement regularly preceded a fit, two questions would still require an answer: (1) What is it produces the paroxysmal increase in cerebral circulation?; and (2) why does not passive cerebral engorgement induced by mechanical means necessarily produce epilepsy?

It has been tentatively queried whether the hearing of music might not produce in some persons sufficient pulmonary hyperventilation to evoke an epileptic response. Some latent epileptic tendency would of course be necessary in such cases. It has been shown by Feleky [15] that various emotional states (such as might be induced by music), and particularly those of wonder and fear, can produce a marked alteration in the depth of breathing and in the inspiration/expiration ratio.

Hypotheses of this character do not bear the imprint of probability and seem far too mechanistic to account adequately for all the clinical phenomena.

From the psychological angle several suggestive points arise for discussion.

In the first place it becomes necessary to examine the suggestion that musicogenic epilepsy is merely a manifestation of hysteria. To many the occurrence of reflex epilepsy of any type raises doubt, and the mere fact that an epileptiform seizure is produced "to order" by the operation of some precipitating factor, may evoke suspicion. It is a clinical commonplace how readily the hysteric will yield to suggestion by immediate unconsciousness. The rôle of music, in precipitating hysterical episodes, is traceable throughout the centuries. In the mediæval epidemics of "dancing mania" or "tarantism," victims would fall unconscious and convulsed at the first notes of the appropriate music. To-day in French West Africa the Senegalese dancer will pass rapidly into an automatic state at the beat of the tom-tom, just as in Tunisia the religious ecstatics will fall foaming to the ground under the influence of their ceremonial music.

Medical literature holds records of comparable cases. Ingegnieros [16] has described a female hysteric of 26, who was a promising violin pupil. Despite the assiduity of her study she failed in her examination, and fell unconscious on hearing the bad news. Thereafter she developed a horror of the violin and would become convulsed whenever she heard that instrument played. This state of affairs was still present ten years later. Redlich, in the paper which has already been mentioned, referred to a second case of convulsive attacks associated with the hearing of orchestral music. This patient proved to be an hysteric, a locksmith whose early aspirations towards a musical career had been frustrated.

The cases of musicogenic epilepsy described in this paper are of a different order. Some of them are accompanied by features which are traditionally regarded as criteria of "organic" as opposed to psychogenic epilepsy. Thus an extensor plantar response has been witnessed and demonstrated in at least two of the cases quoted. Incontinence of urine has occurred in some of the cases, though not in the majority. Such features would suffice, according to the present teaching, to characterize some at least of the attacks of musicogenic epilepsy as being outside the usual picture of hystero-epilepsy.

Whether, however, it is altogether wise, or indeed possible in view of modern conceptions, to attempt to demarcate sharply between "functional" and "organic" epilepsy is arguable. While clinically there are often obvious differences between the majority of attacks of epilepsy on the one hand, and of hysteria on the other, there certainly may occur attacks which cannot readily be assigned to one category or the other. Clinicians are also familiar with the occurrence of hysterical phenomena in a chronic epileptic, and it becomes difficult if not impossible at times to docket individual manifestations as "epileptic" or "non-epileptic." In any event the distinction of "functional" from "organic" is an artificial conception belonging to a past era.

It is tempting to regard musicogenic epilepsy as the operation of a conditioned reflex in the Pavlovian sense. By regarding music as the appropriate analyser, the epileptic manifestations constitute the specific response. A case such as that of Nikitin, where one tune only proved epileptogenous, offers a ready support. The suggestion would also be confirmed if in each patient there were traceable an appropriate musical background on the occasion of the first epileptic attack. Although the clinical information is incomplete in this particular, a single negative finding constitutes an important argument in rebuttal. Again, the occasional occurrence of a seizure without the operation of music, as well as the occasional failure of an attack to follow the usual musical stimulus, are both important arguments against the hypothesis of a conditioned response. We recall furthermore that in Merzheevsky's patient a tune ceased to be epileptogenous once it had lost its novelty.

REFERENCES.

[1] CRITCHLEY, M. "On Reflex Epilepsy." Annual Report of the London County Council, 1933, 4 (Part III), 133.

[2] *Idem.* "Ueber Reflexepilepsie," *Schweiz. Archiv. f. Psych. u. Neur.*, 1935, **35**, 256.

[3] MERZHEEVSKY, I. P. Sloochai epilepsi pripedki kotoroi vizibayootsya nekotopemi musikelnimi tonomi. Minutes Meeting S. Petersburg Soc. Psychiat., 1884.

[4] STEINBRUGGE. Quoted by TRUTOVSKY.

[5] TRUTOVSKY, Y. Y. Epilepsia, proyavlyayoshehayasya pod oliyaneem zvookovik razdrazheni," *Arch. Psych. Neur. i. crimin. psychopath.* (No date.)

[6] Oppenheim, H. "Ueber psychasthenische Krampfe," *Journ. f. Psych. u. Neur.*, 1905-6, **6**, 257.

[7] v. Bechterew, V. "O reflektornoi epilepsi pod oliyaniem evyookovich razdrazheniye," *Obozrenie Psichiat.*, 1914-15, **19**, 513.

[8] Redlich, E. "Kritische Bemerkungen zur Frage der Psychogenese u. Psychotherapie der Epilepsie," *Der Nervenarzt.*, 1929, **2**, 1.

[9] Goldstein, K. "Auslösung epileptischen Anfälle durch Musik (Demonstration)," *Zentralbl. f. d. ges. Neur. u. Psych.*, 1932, **63**, 281.

[10] Nikitin, M. P. "Zur Psychogenese der epileptischen Anfälle," *Der Nervenarzt.*, 1935, **8**, 66.

[11] Erlitzky. Discussion on Professor I. P. Merzheevsky's paper.

[12] Gibbs, F. A., Lennox, W. G., and Gibbs, E. L. "Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man," *Arch. Neur. Psych.*, 1934, **32**, 257.

[13] Diserens, C. M. "The Influence of Music on Behaviour," 1926.

[14] Schoen, M. "The Effects of Music."

[15] Feleky, A. *Journ. Exper. Psych.*, 1916, **1**, 218.

[16] Ingegnieros, J. "La Langage musical et ses troubles hysteriques." Études de Psychol. cliniques. Paris: 1907.

SHIVERING: A CLINICAL STUDY OF THE INFLUENCE OF SENSATION.[1]

BY R. JUNG (FREIBURG), J. DOUPE (WINNIPEG), AND E. ARNOLD CARMICHAEL.

OF the different mechanisms for the regulation of body temperature, shivering may be readily observed and is of some theoretical interest. In a paper by Uprus, Gaylor and Carmichael (1935) a method was described for inducing shivering in the human by the immersion of limbs in cold water. While it was shown that alteration in blood temperature played a prominent part in the production of the shivering, it was not possible to determine if the falling blood temperature acted directly on a "centre," or on a thermo-sensory mechanism capable of stimulating the shivering "centre." As Sherrington (1924) had discussed the part played by cold sensations in the production of shivering in animals, it was considered worth while to attempt to produce shivering in the human by a cold sensory stimulus and to investigate further the possible part played by sensation in the shivering following immersion of limbs in cold water. It is the purpose of this paper to describe the nature of the investigations, the results obtained, and to discuss the latter.

METHOD.

The subject was seated in a comfortable chair with the whole body exposed to the surrounding air. A draught-free tent was then built around the subject with blankets, through which the head alone protruded. The air within the tent was rapidly warmed by means of electric heaters to a stable temperature of 30° C. When the subject felt warm, his peripheral blood-vessels had dilated and the rectal temperature, which was taken by a thermo-junction, had become stable or was rising slightly, the blankets were quickly removed. At the same moment a blower made from the torso of a vacuum cleaner was turned on and blew ice-cooled air at 10 to 15° C. over the naked subject. When

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[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, W.C., while Dr. R. Jung held a Rockefeller Foundation Fellowship, and Dr. J. Doupe a Halley-Stewart Research Fellowship.

the shivering, which commenced shortly following this stimulus, became generalized and uncontrollable, the blower was turned off and radiant heat from an electric lamp was applied to the body until shivering ceased. This procedure was repeated several times on most subjects.

During the investigation the rectal temperature was recorded every fifteen seconds by means of a specially designed thermo-junction situated 5 cm. within the external sphincter. The alterations of temperature at this site were considered as indicating those of the circulating arterial blood for the following reasons. When a normal subject immerses the legs in water at 44 to 45° C. the rectal temperature commences to rise five to ten minutes before evidence of dilatation of the limb vessels takes place. If the legs are then transferred to tanks of water at 15° C. or below the rectal temperature falls. If with the subject well wrapped up in several layers of blankets to include the legs and feet so as to prevent any heat loss, the arms are placed in warm water, a rise in rectal temperature occurs. After transferring the arms to tanks of water at under 15° C. a similar fall of rectal temperature takes place as when the legs are immersed in cold water. It is unlikely, therefore, that the fall in rectal temperature depends upon the local effect of cooled venous blood returning from the legs when the legs are immersed in cold water. The site of the thermo-junction—5 cm. within the anal sphincter—also precludes such a possibility on anatomical grounds. Thus the alterations in rectal temperature as recorded in these investigations indicate the direction of change of arterial blood temperature. Accordingly the rectal temperature will be referred to hereafter as the blood temperature. In the course of some investigations the recording of the blood temperature has been supplemented by skin temperature readings from different areas and by photographic records of the finger volume. Direct observation was made as to the time of onset and cessation of the shivering, its character and the connected phenomena such as goose skin, alteration in skin colour, &c. The subjects were requested to describe any subjective sensations experienced during the investigations.

Thirty-two observations were made on twenty-seven subjects with lesions of the nervous system. Of these, nine suffered from the effect of a local lesion of one cerebral hemisphere. Four subjects had transverse lesions of the spinal cord, but in only one did the disease process completely destroy the function of the spinal cord below the level of its site. Cases of myasthenia, catatonia, Huntington's chorea, Friedreich's ataxia, cerebellar tumour, tabes dorsalis and dyspituitarism were also investigated. Five normal healthy young adults served as controls to the above subjects. Only male subjects were used, except for one young female adult, who had a lesion destroying the spinal cord below the 4th and 5th dorsal segments. The investigations were carried out in spring and autumn, and discontinued during July, August and September, as a sufficiently cool atmosphere was not then available. Reference will also be made to the records which were used for the previous paper. The shivering response elicited by the described method of cooling with cold air will be referred to as "sensory shivering." On the other hand, the shivering response induced by the immersion of the legs in cold water with a subsequent fall in the blood temperature will be called "blood temperature shivering."

RESULTS.

A.—Normals.

Following exposure to the air of the room and the blowing of cold air over the body, shivering commenced in from a quarter to five minutes. This shivering response could be elicited not only during a slight fall in blood temperature but also when the blood temperature was stable or even rising. In any one experiment the changes of blood temperature were insignificant, the fall seldom being more than 0·01° C. and the rise more than 0·02° C. In all instances the shivering ceased almost immediately following the stopping of the blower and the application of radiant heat to the body. Thus shivering was produced in normal subjects by a cold sensory stimulus to a wide area of skin and was found to be independent of the direction of blood temperature change: further, the application of a warm cutaneous stimulus immediately on cessation of the cold draught caused the shivering to stop forthwith.

B.—Abnormals.

A general survey of all the investigations showed that the facility of producing sensory shivering varied widely in different individuals: a short latent period and a long prolongation of shivering after cessation of the cold stimulus were seen in subjects with differently situated lesions of the nervous system, as well as in normal persons. It appeared that the facility to shiver was dependent more on the general physical condition (increased readiness to shiver in ill and poorly nourished individuals and the opposite in strong and fat persons) rather than on the presence of any focal lesion of the nervous system. Even in deeply stuperous catatonic patients sensory shivering as well as blood temperature shivering could be elicited by adequate stimuli. Nearly half the observations were done in the morning when the subjects had a relatively low body temperature (generally below 37° C.) and the remainder in the afternoon with a relatively high body temperature (generally above 37° C.). No conspicuous differences in the time of onset of shivering could be observed in these two groups, so that it may be assumed that sensory shivering is independent of the actual blood temperature, provided it has not been artificially lowered.

C.—*Afferent Mechanism.*

That the stimulus for the shivering was in fact the sensory cold stimulus was demonstrated as follows. The subject with destruction of the spinal cord and consequent anæsthesia below the level of the lesion was submitted to the following procedure. During a gradual fall of 0·02° C. in blood temperature, the insentient part of the body was exposed to the cold air draught for seven minutes; no shivering resulted. The blood temperature then commenced to rise and while in this state the sentient part of the body was exposed to the cold stream of air; within a minute and a half shivering limited to the muscles innervated from above the level of the lesion, commenced and continued until the blower was turned off and radiant heat applied. While the cold air was directed on to the normal skin, the subject complained of coldness, saying "It is cold." The cold sensation was referred to the surface of the sentient skin. Immediately the radiant heat was applied, the cold sensation rapidly changed to one of warmth.

From these observations it was apparent that a cold cutaneous sensation produced shivering and that a similar stimulus to an anæsthetic region failed to give rise to shivering. Thus the shivering produced by a stream of cold air was dependent upon afferent impulses coming from the skin.

To determine if hyperæsthesia to cold in any way modified the shivering responses, two subjects were investigated, one suffering tabes dorsalis and the other from a lesion of the thalamus. T subjects marked hyperæsthesia to cold was demonstrable The stream of cold air caused the subject with tabes to jump as if he felt it as an almost painful stimulus. Shiverin not commence for four and a half minutes and ceased the blower was turned off and the radiant heat app period the blood temperature rose 0·01° C. At stable rectal temperature, shivering was produced within one and a half minutes. In the subject with a lesion of the thalamus shivering resulted one minute after the application of the cold air and ceased within two minutes of the application of the radiant heat. In neither subject was the shivering more intense than in the normal.

Thus hyperæsthesia to cold does not alter significantly the time of onset of shivering following the application of a stream of cold air to the body.

D.—Efferent Mechanism.

Spinal lesions.—It has been shown that following the sensory stimulus of cold to the sentient parts of the subject with a complete lesion of the spinal cord, shivering only occurred in the muscles innervated from above the level of the lesion. Similar observations were made on two other subjects with transverse lesions of the spinal cord following fracture of the vertebræ. On two occasions a subject, in whom the spinothalamic tracts had been severed at operation for the relief of pain, was exposed to the stream of cold air. This caused shivering, though on each occasion there was a rising blood temperature. Both times the shivering was limited to the muscles receiving a nerve supply from segments above the level of the incisions in the spinal cord. Sensory shivering is therefore limited to muscles receiving a nerve supply from above the level of a complete lesion of the spinal cord or above the level of section of the antero-lateral columns.

Pyramidal lesions.—In eight subjects with damage to either one or both pyramidal tracts sensory shivering was provoked and occurred in all the muscles of the arms, trunk and legs.

From these observations it is apparent that shivering is independent of the integrity of the pyramidal tract and is absent below the severance of the anterolateral columns. Sensory shivering has for its production the same efferent pathways within the spinal cord as blood temperature shivering; these pathways lie in the anterolateral region of the spinal cord.

further study was made of the effect of lesions situated elsewhere
the spinal cord on sensory shivering.

ar lesions.—In a subject suffering from Friedreich's ataxia,
sensory shivering was produced during a slight rise in
ure, it was found that in place of the clonus-like move-
normal subject the movements were irregular and were
horeiform. These choreiform movements were also
ith a cerebellar tumour when they were limited

to the limbs on the same side as the tumour. That the integrity of cerebellar function is necessary for the production of the clonus-like movements of shivering is the deduction made from these observations.

Defective deep sensibility.—When the subject with tabes, who exhibited deep sensory loss in the legs including the senses of position and passive movement, was investigated, the cold stream of air produced well-marked clonus-like movements in the arms; but in the legs the movements were more irregular and jerk-like, varying considerably in range, and were later in onset. Thus absence of deep sensation from a limb altered the time of onset and character of the movement of shivering. Summarized, the clonus-like movements of shivering require the functioning of the cerebellum, its connections and the afferents coming from the muscles.

Lesions of the cerebral hemisphere.—Nine subjects, each with a discrete lesion limited to a cerebral hemisphere, were examined. The lesions in each individual varied as to site, but in one or other subject all areas of the cerebral substance were included. In two subjects it was only possible to produce sensory shivering when there was a slight fall of blood temperature; in the other seven, sensory shivering occurred during a rise in blood temperature or while it remained stable. Though no preference for one side or the other to present shivering early was constantly observed, sensory shivering tended to show itself more constantly and a few seconds earlier in the muscles of the limbs which were spastic. It was similarly noticed that in subjects suffering from amyotrophic lateral sclerosis the muscles of the limbs exhibiting marked spasticity showed the clonus-like shivering movements more readily than the others. In assessing the effect of lesions of the pyramidal tract on sensory shivering, it should be remembered that variations in posture of a normal subject will affect the time of onset and the degree of shivering. Thus no conclusive evidence could be obtained from the study of this series that sensory shivering was in any way influenced by lesions of the cerebral hemispheres, apart from the fact that muscles of any spastic limb tend to show clonus-like movements easily.

E.—Relationship between Sensory Shivering and Blood Temperature.

For a detailed study of the influence of sensation on shivering and the relationship of the shivering produced by the two methods, a subject with complete anæsthesia below the 4th and 6th dorsal segments was investigated. It has already been demonstrated that the sensation of cold caused shivering in this subject while the rectal temperature was rising slightly. On another occasion shivering was initiated by blowing cold air over the sentient parts of the body during which there was a slight fall of 0·02° C. in the blood temperature. This shivering was then stopped by the application of radiant heat to sentient parts of the body, and when the shivering ceased the anæsthetic legs were placed in a tank of water at 13° C. During the next thirty minutes the rectal temperature fell 0·7° C., but as long as the radiant heat remained applied to the upper part of the body, no shivering occurred. After a fall of blood temperature of 0·4° C. the subject complained of an internal cold sensation in the chest, which gradually increased to a feeling of "cold through and through." She said, "I am cold." The blood temperature, having fallen 0·7° C. began to rise, presumably owing to some internal heat-regulating mechanism, as the legs were still immersed in cold water. At the time of cessation of fall of blood temperature a few fibrillary twitches lasting less than half a minute were observed in the pectoral muscles. As the blood temperature rose, the cold internal sensation disappeared. From these observations it may be deduced that a fall in blood temperature and an internal cold feeling need not necessarily be followed by shivering when at the same time the sentient areas of the body are exposed to a warm stimulus.

The same subject was investigated further. With the face, upper limbs and chest uncovered, the anæsthetic legs were immersed in a tank of water at 42° C., which produced a rise in blood temperature of 0·3° C. The legs were then transferred to water at 9° C. with the result that two minutes later the blood temperature began to fall rapidly. Eight minutes later, after a fall in blood temperature of 0·63° C. shivering commenced and rapidly became generalized and uncontrollable. Several radiant heat lamps were then switched on and directed to the exposed and sentient parts of the body. During the course of the next eight minutes the shivering gradually became less and eventually ceased altogether, though the blood temperature had continued to fall a further 0·65° C. At this stage the subject ceased to feel cold on the surface of the body though she appreciated a cold internal sensation. The lights were then switched off and within thirty seconds the shivering recommenced, becoming as severe as before, and the subject complained of feeling cold all over. The legs were then transferred to water at 42° C., which caused a rise of blood temperature after an interval of four minutes. The shivering continued, but gradually became less, ceasing altogether when the blood temperature had risen 0·7° C. from its lowest point. During the fall in blood temperature and irrespective of the warmth applied to the surface by the radiant heat lamps, the subject felt a cold internal sensation.

From these observations it is apparent that the shivering accompanying a fall in blood temperature may be completely abolished by a warm stimulus applied to the sentient parts of the body. Thus an adequate warm cutaneous sensation will inhibit shivering, though the blood temperature is falling and there is an internal feeling of cold.

An attempt was then made to induce shivering during a rise in blood temperature. For this purpose the legs were immersed in water at 42° C.; which caused a rise of 0·35° C. in blood temperature in twenty minutes. While the blood temperature was rising, the stream of cold air was applied to the upper parts of the body. This resulted in shivering occurring two minutes later on one occasion and three and a half minutes later on another occasion. The second time, immediately the stream of cold air ceased and radiant heat was applied, the shivering stopped. At this point the legs were removed from the tank of warm water and the blood temperature allowed to fall slowly. The stream of cold air was then applied and within one minute shivering commenced.

That the shivering response produced by a stream of cold air may still be obtained though the blood temperature is rising is apparent from these observations. It is also to be noted that sensory shivering was more easily produced when the blood temperature was falling.

As these observations had shown that the shivering associated with a rapid fall in blood temperature could be inhibited by a continuous warm stimulus, an attempt was made to produce in a normal subject a fall in blood temperature without applying a severe cold cutaneous stimulus. On several occasions shivering was produced in one subject by the immersion of the lower limbs in cold water at 9° to 12° C. With a room temperature of 22° C. immersion of the legs in cold water at 9·1° C. was followed three minutes later by shivering, the blood temperature having fallen 0·06° C.; again, with a room temperature of 36·5° C. immersion of the legs in cold water at 12·1° C. resulted in shivering six minutes later, though a fall of only 0·03° C. had taken place in blood temperature. Thus with a warm or cold surrounding temperature shivering was easily provoked by plunging the legs into cold water. To determine if the fall in blood temperature was the provoking agent rather than the cold cutaneous stimulus resulting from the immersion of the legs in water at 9° to 12° C., the following investigation was carried out. The same subject, after a preliminary period of warming, transferred the legs from the bath of water at 44·5° C. to one of water at 30·5° C. The subject stated that the water felt "cool" but not cold. Within eight minutes the blood temperature had fallen 0·32° C., without any shivering. At the end of this period the legs were immersed in water at 15° C., whereupon shivering immediately commenced. The sensation following immersion at this lower temperature was described as "very cold."

As in the first two experiments a fall of blood temperature of 0·06° C. or less was followed by shivering and in the last experiment a fall of 0·32° C. was not followed by shivering, the shivering could hardly result from the falling blood temperature. The factor, common to all these experiments and followed by shivering, was the immersion of the legs in cold water at 15° C. or below. Therefore the cutaneous sensation of cold was apparently the provoking stimulus in this subject.

Finally the records of previous experiments set forth in the earlier paper were reviewed. It was found that with insentient legs immersed in cold water shivering only occurred after a fall of 0·5° C. in blood temperature, while in normal subjects a fall of 0·1° C. was followed by shivering. Similar observations were made in the present series. The marked difference in the time of onset of shivering between those with normal sensation in the legs and those without indicates further that when the legs of the normal subject are immersed in cold water the resultant shivering is dependent more upon the sensation of cold from the legs than on the fall of blood temperature.

DISCUSSION.

In addition to shivering produced by immersion of the limbs in cold water it has been possible to provoke shivering in subjects by cooling the surface of the body with cold air. The shivering so provoked occurred during a stable blood temperature or even when the blood temperature was slowly rising. Therefore a causative factor of shivering other than changes in blood temperature had to be assumed. As the shivering followed a cold stimulus to the skin it appeared that this was the factor. This assumption was shown to be correct, for a stream of cold air produced shivering when directed on to normal skin and no shivering when directed on to anæsthetic skin.

The motor characters of the shivering produced by the sensory stimulus of cold air both in the normal and pathological subjects were essentially the same as those of shivering following immersion of limbs in cold water. The presence of shivering in subjects with lesions of the pyramidal tracts indicated that sensory shivering was independent of the integrity of these tracts. As sensory shivering was absent below the level of the incision of the antero-lateral columns in the spinal cord, it is necessary to postulate that the efferent pathway for shivering lies in this region of the spinal cord. In this respect the efferent pathway for sensory shivering is the same as for blood temperature shivering. It has been further shown that the character of sensory shivering is modified by lesions of the cerebellum and its connections, again resembling blood temperature shivering. It may therefore be presumed that the two methods of provoking shivering both require the same efferent pathway and the integrity of the cerebellar mechanism for its clonus-like character. It has further been shown that the clonus-like character is altered by a lesion of the sensory fibres from the limbs.

Lastly, it has been shown that lesions of the substance of the cerebral hemisphere do not significantly alter the shivering response to a stream of cold air—thus having a similarity to blood temperature shivering. In experiments on animals Pinkston, Bard and Rioch (1934) observed that shivering occurred more readily after bilateral ablation of the fore-brain. They also noted in a limited number of experiments that following unilateral ablation shivering "was entirely symmetrical." With the latter observation those in the present paper are in agreement. Aring (1935) reported that in monkeys and baboons there was a "significant deviation" of the shivering responses following removal of "motor area (Area 4)." In these animals shivering was more easily provoked but remained symmetrical. The symmetry of the shivering responses in man with hemiplegia is in accord with these animal experiments.

It is now necessary to determine if the underlying affector mechanism be the same or different in the two methods of producing shivering. The part played by sensation in the production of shivering has been discussed by several authors. Sherrington (1924) believed from his experiments on dogs that changes in blood temperature played a prominent part in the production of shivering. On the other hand, Liebermeister (1860), Ebbecke (1917) and others considered that the heat-regulating mechanism of the body, including shivering, were dependent for their delicate control on sensory impulses. In the investigations reported in this paper it has been shown that shivering associated with a fall in blood temperature produced by the immersion of anæsthetic legs in cold water may be inhibited completely by a warm sensory stimulus, or once provoked, can be stopped by a warm cutaneous stimulus, although the blood temperature continues to fall. Again, in subjects with absence of sensation in the legs, shivering only follows a fall of 0·5° C. in blood temperature when the legs are immersed in cold water; at this period the subject feels cold. On the other hand, in normal subjects a fall of only 0·1° C. in blood temperature is associated with shivering when a cutaneous sensation from the cold water accompanies the fall: if, however, this intense cold sensory stimulus is avoided by immersing the legs in water at 30·5° C. a greater fall in blood temperature occurs without shivering. Further, it has been shown that shivering can be provoked during a rise in blood temperature by a cold sensory stimulus. For these reasons it appears that sensory impulses are much more productive of shivering than a fall in blood temperature. In fact, it is only in very extreme circumstances that a fall in blood temperature of a sufficient degree will alone produce shivering and when it does the subject has experienced a subjective sensation of internal cold, which suggests that sensory afferents are already in play. These observations, therefore, favour the view that the sensory impulses of cold from a wide area of the body comprise the effective stimulus for shivering when it is provoked either by immersion of the limbs in cold water or by a stream of cold air applied to the body.

SUMMARY.

A method has been described of provoking shivering without lowering the blood temperature.

Shivering so provoked has the same characters as shivering associated with a fall in blood temperature. The efferent pathways are the same.

Evidence has been produced which favours the view that shivering, associated with a rapid fall in blood temperature, results from sensory impulses rather than from changes in blood temperature directly acting on a "centre."

We desire to express our thanks to those members of the Honorary Staff of the Hospital who so kindly permitted observations to be made on patients under their care. Dr. C. D. Aring kindly assisted in several of the investigations and for his help we are grateful.

REFERENCES.

ARING, C. D. *Amer. Journ. Physiol.*, 1935, **113**, 8.
EBBECKE, U. *Pfluger's Archiv.*, 1917, **169**, 395.
LIEBERMEISTER, C. *Arch Anat. Physiol*, 1860, 520.
PINKSTON, J. O., BARD, P., and RIOCH, D M. *Amer. Journ. Physiol.*, 1934, **109**, 515.
SHERRINGTON, C. S. *Journ. Physiol.*, 1924, **58**, 405.
UPRUS, V., GAYLOR, G. B, and CARMICHAEL, E. A. *Brain*, 1935, **58**, 220.

SYMPATHETIC GANGLIONIC RESPONSES IN MAN.[1]

BY B. BOLTON, D. J. WILLIAMS, AND E. ARNOLD CARMICHAEL.

BEFORE making a study of the possible part played in man by the spinal segments in vasomotor responses, it is necessary to determine if there is a response dependent upon an afferent fibre which passes direct to the sympathetic ganglion and is there in synaptic connection with the efferent cells. It is the purpose of this paper to describe the investigations undertaken and to discuss the results obtained.

METHOD.

In two subjects plethysmographic records were taken from the digits of the hands and feet by a method previously described by Bolton, Carmichael and Stürup (1936). Vasomotor responses were elicited by various sensory stimuli while the subject was in both a cold and a warm state.

OBSERVATIONS.

Subject A., aged 16. Nine months before admission to hospital, during the course of twenty-four hours, she developed a complete paralysis of both legs. On examination the legs were found to be in a flaccid state with no tendon reflexes. The muscles of the lower abdominal wall, thighs, calves and feet were wasted. There was a complete loss of all forms of sensation up to the lower level of the 5th dorsal segment on the right side, and the 4th dorsal segment on the left side.

Local injury to the skin of the abdomen, thigh and calves, as produced by stroking with a blunt pencil, caused a well-marked flare. Faradic stimulation of the skin over these areas resulted in a pilomotor response over an area of roughly 3 cm. diameter. The flare following injury indicated that the posterior root ganglia and the peripheral portion of the sensory nerves were undamaged; further, the post-ganglionic pilomotor fibres were also intact, otherwise it would not have been possible to obtain a faradic pilomotor response. When exposed to the atmosphere of a cold room at 17° C., and following immersion of the left upper limb in a tank of cold water which caused a drop of 0·45° C. in rectal temperature in twelve minutes, the temperature of the toes remained between 33° and 34° C. Such a procedure caused a fall in temperature of the fingers of the right hand from 33° to 25° C., when the experiment was terminated. The persistent dilatation of the vessels of the toes, as indicated by a steady skin temperature of 33° C., may result from interruption of either the pre-ganglionic or post-ganglionic fibres to the vessels of the toes. It has been shown in this subject that the post-ganglionic pilomotor fibres were still present. As the cell stations for the pilomotor post-ganglionic fibres are in the sympathetic ganglia, these sympathetic ganglia must necessarily be intact. Also situated in the sympathetic ganglia are the cells of the vasomotor post-ganglionic fibres; it may accordingly be deduced that in this subject these post-ganglionic vasomotor fibres were also intact. The persistent state of dilatation of the vessels of the toes was therefore dependent upon an interruption of the pre-ganglionic fibres or to a destruction of the cells of these fibres as they lay in the lateral horn of the spinal cord. As the lesion from clinical evidence was essentially spinal, it was more likely that the latter event was the correct one. In favour of this was the observation that the muscles of the abdomen and legs were wasted, the result of destruction of the anterior horn cells. In this subject, then, it may be safely deduced that there was an intact peripheral sympathetic ganglionic system. As the sensory peripheral fibres were also intact, this subject was ideal for the study of possible ganglionic responses.

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[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, W.C., while Dr. D. J. Williams held a Halley-Stewart Research Fellowship.

In a warm state, plethysmographic records were obtained from the digits of one hand and both great toes. Stimulation of the skin with a nerve supply from above the level of the spinal lesion caused vasoconstriction only in the finger. When similar stimuli were applied to the anæsthetic skin, no responses were obtained either in the fingers or in the toes. Severe pressure of the leg muscles and distension of the rectum by a balloon produced no effect in toe volume; further, during long periods of an hour or more no variation of toe volume occurred, though during these periods active intestinal movements were present, as evidenced by marked borborygmi. Thus in this subject it was not possible with the stimuli used to produce a response in the legs. This interpreted indicated that no stimulus could reach the sympathetic ganglia direct by an afferent fibre and there stimulate the sympathetic vasomotor cells. In other words, there was no ganglionic response.

Subject B., aged 24. In an accident he was injured in the lumbar region, where there was X-ray evidence of a fracture dislocation of the 1st and 2nd lumbar vertebræ. As a result of this injury there was a flaccid paralysis of the legs, with wasting of the muscles of the feet, calves and left quadriceps. The ankle and knee jerks were absent. All forms of sensation were lost on the left side over the distribution of lumbar 2nd root, the remaining lumbar and sacral roots and on the right side from and including the 4th lumbar root. At operation the roots of the cauda equina were found matted together and grey, some actually being torn.

Following a local injury, as produced by drawing a blunt object fairly heavily along the surface of the insensitive areas of the skin, a definite flare developed. The presence of the flare indicated that the posterior root ganglia cells and the peripheral portion of the sensory nerves to the anæsthetic skin were also intact. When this subject was warmed by immersing the upper limb in a tank of water at 44 to 45° C., which produced an adequate rise in rectal temperature, the temperature of the two big toes exposed to a room temperature of 21° C. rose rapidly after a period of four minutes and reached a temperature of 33° C. in nine minutes. When the upper limb was transferred to a tank of water at 12° C. the temperature of the toes fell rapidly. In this way it was possible to demonstrate that the blood-vessels of the toes were under the control of the sympathetic vasomotor nerves; in other words, no damage had occurred to the vasomotor pre-ganglionic fibres emerging in the lower dorsal and first lumbar anterior roots, to the sympathetic ganglia or to the post-ganglionic fibres to the vessels of the toes. The wasting of the muscles of the legs followed upon the destruction of the anterior roots as they lay in the spinal canal. In this subject, then, the pre-ganglionic and post-ganglionic fibres were intact, but the path for afferent impulses from the legs was interrupted central to the posterior root ganglion, leaving the peripheral part of the sensory neurone intact. This second subject permitted a further investigation for ganglionic responses as the nervous control of the blood vessels of the toes was intact.

The subject was then examined for vasomotor responses in the vessels of the large toes and an index finger. In a cool state with the peripheral blood-vessels constricted and in a warm state with the vessels dilated, various sensory stimuli were applied to the normal and anæsthetic skin areas. In the cold state no alterations of the plethysmographic records were obtained, irrespective of the site or nature of the sensory stimulus. In the warm state, stimuli such as a pinch, pressure and cold applied to the normally sensitive skin produced a vasoconstrictor response in the digits of the hand and both feet. Visceral pain from pressure of the testicle resulted in similar vasoconstriction. When the anæsthetic area was stimulated by stronger stimuli, including severe deep pressure, no responses occurred in the digits of either the upper or lower limbs; stimulation of the dorsalis pedis artery on the one side by a faradic current produced no response in the digits of the other lower limb; similarly, stimulation of the terminal branch of the anterior tibial nerve on the same side failed to produce vasoconstriction in a digit of any limb, including the limb stimulated. Thus in this subject stimulation of the lower limb failed to produce any vasomotor response either in that limb or in the upper limb.

As the examination of the subject had demonstrated no lesion outside the spinal canal, it appears that if an afferent fibre coming from the legs terminates within the sympathetic ganglia supplying the leg, it has been impossible to bring it into functional activity by the methods employed. Thus no sympathetic ganglionic responses were demonstrable in this subject. That vasoconstrictor responses could be obtained in the toes following stimulation of the sentient parts of the body indicates that the afferent impulses pass centrally to the cells in the lateral horn in the spinal cord either directly or via several neurones. There, stimulation of the lateral horn cells causes impulses to pass out to the motor cells in the sympathetic ganglia, the activity of which causes vasoconstriction. The absence of responses by stimulating the legs in this subject and the presence of the responses by stimulating normal skin clearly indicates that vasomotor responses are dependent upon an arc, which includes elements within the central nervous system.

DISCUSSION.

In recent years renewed attention has been paid to the possibility of synaptic connections between afferents and sympathetic efferents within sympathetic ganglia. Schwartz (1934), using the psycho-galvanic reflex (skin resistance), demonstrated an alteration in the reflex when pressure was made on a limb which had been de-afferented and had had all the white rami going to its sympathetic ganglia cut. When all the grey rami were also cut, no response occurred, but the skin resistance by this procedure had risen from 8,000 to 15,000 ohms. The results which he obtained do not necessarily indicate a ganglionic reflex and are explicable upon a basis of altered circulation produced by the pressure on the limb, for Goadby and Goadby (1936) showed that the psycho-galvanic reflex (skin resistance) was dependent upon the blood supply and was not necessarily evidence of a nervous reflex. Wernøe (1925) deduced from his experiments on fish that a sympathetic ganglion cell might have two neurones; one passing to the gut wall and the other to the integument, both being motor. Following stimulation of the gut, alteration of pigment distribution took place in the periphery. It is difficult to accept this hypothesis as it means a motor ending may also act as a sensory ending. On the other hand Bain, Irving and McSwiney (1935) have shown in a series of carefully controlled experiments on cats that there is no synaptic connection between an afferent fibre from the gut and the cells within the sympathetic ganglia.

The experiments described reveal results in line with this last viewpoint. In the first subject with intact sympathetic ganglia and peripheral sensory neurones, but a damaged spinal cord destroying the cells in the lateral horn it was impossible to produce any vasomotor responses in the legs. In the second subject, in whom it was possible to demonstrate that the sympathetic ganglia were functionally intact and in whom the afferent fibres were destroyed as they entered the cord without damage to the cord, again no vasomotor responses were obtainable by stimulating the anæsthetic zone. Thus, to produce in man a vasomotor response it is necessary for the afferent fibre to reach the spinal cord and within the central nervous system to connect either directly or by connector neurones to the cells of the lateral horn. It has not been possible to produce a vasomotor response when sensory neurones and sympathetic ganglia were intact and the cord or attachment of the sensory neurone to the cord destroyed. This indicates that no ganglionic vasomotor responses in man could be obtained.

SUMMARY.

In man no evidence has been obtained to favour the presence of ganglionic vasomotor responses.

REFERENCES.

Bain, W. A., Irving, J. T., and McSwiney, B. A. *Journ. Physiol.*, 1935, **84**, 323.
Bolton, B., Carmichael, E. Arnold and Sturup, G. *Ibid.*, 1936, **86**, 83.
Goadby, K., and Goadby, H. *Proc. Phys. Soc.*; *Journ. Physiol.*, 1936, **86**, 11 P.
Schwartz, H. G. *Amer. Journ. Physiol.*, 1934, **109**. 593.
Wernøe, Th. B. *Pflugers Arch.*, 1925, **210**, 1.

THE ORIGIN AND MECHANISM OF PAROXYSMAL NEURALGIC PAIN AND THE SURGICAL TREATMENT OF CENTRAL PAIN.

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Is it justifiable to regard neuralgic pain as a specific unit? This seemed to have been the case when Henle [4] in 1853 wrote : "Neuralgia means pain for the explanation of which a lesion of the corresponding peripheral nerve cannot be demonstrated." Histological methods have since improved and simultaneously our knowledge of the pathology of the nervous system. At present the trend is to add more and more cases, previously diagnosed as neuralgia, to the chapter of neuritis. In the new edition of the "Handbuch der Neurologie" [6] (1935) the title "neuralgia" is confined to typical and atypical trigeminal neuralgia, to occipital, and to some unusual forms of brachial and intercostal neuralgia. Even this arrangement seems to require some sort of apology, for absence of pathological changes in the methods of to-day may not mean the same in the technique of to-morrow. And should we not assume the origin of neuralgia pain to be in the peripheral nervous system, realizing that section of the nerve, distal or proximal to its ganglion, relieves the pain permanently?

Careful examination of patients with trigeminal neuralgia, with tabetic crises or with thalamic pain, however, must convince the observer that the characteristic symptoms and signs of this group are entirely different from those caused by the neurolytic swelling of so-called neuritis.

Pain plays an important part in medicine. New ways and means of surgical intervention for relief of pain not thought of a half century ago, have been discovered and described (retrogasserian neurotomy, cordotomy, rhizotomy). The basic problems of the physiology of pain, however, are not yet solved. This is understandable when it is considered that pain and its characteristics are purely subjective phenomena. The possibility of experimental investigation in animals is limited. We may try to find a point of attack through careful analysis of patients showing disturbances of sensibility, but we are also bound to seek opportunities to observe the course of physiological experiments presented by nature itself.

In 1934, by means of graduated hairs and thorns and by chronaximetry, we examined the sensibility of fifty patients suffering from trigeminal neuralgia before and after retrogasserian neurotomy [5]. The results suggested the presence of lesions situated in the thalamo-cortical sensory system. Serial anatomical examination of the brain-stem in three cases seemed to corroborate this hypothesis. Various considerations and clinical data fitted well into this assumption, but we hesitated to base a positive conclusion upon three cases, and the chance of obtaining additional autopsy material in an operation with a mortality of less than one half of one per cent. was small. We were fortunate, however, in having an opportunity to observe a patient whose treatment enabled us to confirm our conception of the origin of trigeminal pain from an entirely different angle. Beyond this special problem of facial neuralgia we got a first glimpse into the mechanism of central pain as a whole, and could attempt its relief.

CASE REPORT.

Mrs. K. (File No. 31606), aged 64, a very intelligent woman, for twenty-five years following acute muscular rheumatism suffered from high blood-pressure (210/100) accompanied by myocardial degeneration, diabetes, headache, scintillating scotoma, and pains in the eyes, until in 1933 she had a "stroke." At that time she developed a complete left-sided hemiplegia with dysarthria, and immediate excruciating pain in the entire left side of her body from the vertex over her face, thorax, abdomen, and extremities down to the toes. While the hemiplegia and dysarthria improved to practically normal function, the pain persisted and defied all therapy. At the time of her admission to the Hospital of the University of Pennsylvania the patient was consuming up to 9 gr. of morphine daily without complete relief of pain.

Two forms of pain were differentiated by the patient:—

(1) A constant intense pain "as if red-hot lava were running over her shoulder, hands and toes," or "as if hot lead were being poured into the palm of her hand." At the left side of her face she felt a "sensation as if icy water was trickling over the cheek," or "as if an ice plate was being pressed against the face." At other times the fingers of the left hand and the left side of the trunk, especially in the lower quadrant, "felt as though they had been smashed with a hammer." All over the left side was an excruciating sensation "as if the skin were drawn just as tight as could be."

(2) Twice or three times a day a paroxysm occurred during which the patient experienced electric shocks passing through the left side of the body.

Despite this spontaneous pain and dysæsthesia there was an extensive though not complete anæsthesia and analgesia of the entire left side, with loss of position sense and with astereognosis. Some scattered touch and pain points were elicitable and showed increased threshold, explosive reaction, long after-effect and wide radiation of the pain.

Most of the sensation, wherever elicited, was referred to the left upper arm and shoulder, but was not localized at all. The perception of the stimuli was inadequate quantitatively and qualitatively. Slight rubbing of the left sole, for example, was felt as an intense pain either "somewhere up in the thigh or shoulder," or without localization.

Pain sensation was slightly decreased over the right extremities also.

Chronaximetrically the rheobase was equally high but stable on both sides, the chronaxie high and increasing, with repeated stimuli on both sides, but much more on the left.

The patient's mental faculties were dulled by suffering and opiates. Her interests were limited to her pain and its relief, and she was insistent upon any type of operation which offered the slightest hope of alleviating her discomforts.

In our therapeutic considerations we were guided by our above-mentioned experience with major trigeminal neuralgia. If that assumption held true, blocking of the 5th nerve should in this case also relieve the pain in the face. On May 27, 1935, alcohol was injected into the left gasserian ganglion with immediate and complete relief of all pain and all paræsthesias in the three divisions of the 5th nerve, while the adjacent area of C2-3 became more painful than ever. Although the face was almost anæsthetic and analgesic before the alcohol injection, the patient complained of numbness after the injection.

Since interruption of the cranial nerve had proven so helpful in relieving pain, the next step was to try the effect of spinal anæsthesia. To our surprise this procedure, though effective on the right side, increased considerably the pain in the left leg for the time of its duration. The two experiments, of course, were not equivalent, as the sensitivity of the 5th nerve includes only part of the tactile sensation. The varying result may be explained in accordance with the experience that a lesion of Goll's and Burdach's tracts produced or increased pain, as demonstrated by Brown-Séquard [1].

Following this negative result we suggested a cordotomy. On July 3, 1935, the right anterolateral column was divided in the fifth cervical segment. At the same time, the second and third left posterior cervical roots were crushed. The cordotomy itself was unusually painful.

For about two weeks after operation the patient had gradually decreasing pains in the right arm, presumably from stretching of the posterior roots in turning the cord. But the left side of the body and extremities were completely free from pain and dysæsthesia. Two days after the operation it was possible to cut down the daily dose of morphine from 9 to 2 gr. The patient left the hospital on July 16, 1935, no longer taking morphine, free from pain in her left side, and able to walk. This complete relief continued for another couple of months, when gradually some pain reappeared in the left shoulder and heel but not in the trunk. She remained free of morphine despite her discomfort.

It is well known that in cases of thalamic lesion with pain occurring in attacks, the paroxysm eventually may be elicited by stimulating the healthy side. Therefore, we were not surprised that the unilateral cordotomy was not permanently effective, and accordingly advised the referring physician to send the patient back for cordotomy of the opposite side whenever the pain again should become intolerable.

According to the patient's statement, it was not until about six months after the operation that the pain began to increase considerably.

At that time the alcohol injection of the left trigeminal nerve became ineffective. Late in February, 1936, her physician wrote that "the operation did her a great deal of good and her general condition is as good or better than before the operation."

The patient was readmitted on March 6, 1936, nine months after her first operation. She claimed that for the last four or five weeks the pain had increased rapidly although it was still not as bad as before the operation. The pain was localized in the left hand, shoulder, and heel, the rest of the arm and thigh being fairly free and the trunk completely pain-free. In the face, an area about two inches wide in front of the left ear was particularly sensitive to stimulation, pressure or draught. The pain had changed its character. The peculiar sensations of "hot lead" or "red lava" or "icy water" had disappeared. What was left was an indescribable "pure" burning, throbbing sensation, not an excruciating pain—sometimes absent for days, then again suddenly recurring. Such attacks often occurred during sleep and the patient awoke with pain.

The mental attitude of the patient had improved amazingly. In contradistinction to her behaviour previous to her first operation it was now possible to discuss with her different problems. She was anxious not to spend too much money and explained sensibly how difficult it was to make ends meet because of her long illness. In summary, it was the general opinion of the observers, as well as of the patient, that the discomforts were not nearly so great at this time as on the occasion of her previous admission.

Objectively, the sensibility was, with slight variations, about the same as before the cordotomy. Graphesthesia was now absent on both sides. Finger touch (not hairs up to 20 grm.) were felt all over the left side of the body but could not be localized. They had a disagreeable feeling tone on the face but not on the arm and leg. Stroking the sole was perceived as "tickling."

Pinching the skin was correctly localized from the left hand upward to the elbow. From there up to the shoulder it was referred to the fingers. Exactly the same held true for pin-prick except on the leg. On the thighs thorns of 8 grm./mm. were perceived but could not be identified, while pin-prick at the sole and ankle were correctly localized and somewhat sharp.

Pressure sense was normal on the whole right side and on the left side of the face with 50 to 70 mm. Hg. Pressure of 110 to 150 mm. Hg. "hurt" on the left arm : 200 mm. Hg. was felt over the left side of the chest ; no pressure was felt on the left thigh but 230 mm. Hg. was felt over the left tibia.

Chronaximetrically the right side showed, as it did before cordotomy, normal and stable rheobases and slightly elevated chronaxie figures, increasing with repeated stimulation. On the left side 200 V were not perceived on the face and leg. At the left arm and hand rheobase was normal and stable, chronaxie considerably increased. With long ($\frac{1}{8}$ sec.) and repeated stimuli occasionally the sensation became disagreeable, eventually suddenly "pin-like," but not painful.

On March 10, 1936, a left-sided cordotomy was performed at the level of the first operation, resulting in analgesia of the right side up to the shoulder. The patient's immediate convalescence was somewhat stormy, partly as the result of her precarious kidney function (which barely kept her from uræmia) and partly as the result of unexplained sudden, wide fluctuations of her blood-pressure. This became stabilized at 150 to 180 systolic in a few days and the patient's condition improved.

On March 20, 1936, the left gasserian ganglion was reinjected with alcohol. During the injection the patient experienced a good deal of pain which stopped in a few seconds. Good relief was obtained.

At the time of her discharge the patient had a complete loss of pain and temperature sensation on the right side up to her shoulder and on the whole left side, with the exception of the heel, where deep pin-prick was painful. Subjectively, the patient complained mostly of this spot. It was the general opinion that she had very little severe pain.

As far as we could learn from the report of her family physician the patient's condition continued to improve for a short time and then became more or less stationary. At this time her physician wrote : "I think that she was relieved of a considerable amount of the pain by the two operations performed." On May 29, 1936, she rather rapidly became uræmic and died.

DISCUSSION.

The main interest of this observation, in our opinion, consists in the opportunity to explore some problems of pain physiology in man with the exactness of an animal experiment.

Our starting point was the assumption that trigeminal neuralgia was due to peripheral stimulation of the 5th nerve in the presence of a thalamic lesion. In this particular case, where the pain was undoubtedly of thalamic origin, blocking of the peripheral nerve at the gasserian ganglion gave immediate and complete relief in the distribution of the 5th nerve. We feel, therefore, that this experience represents a further corroboration of our premise as far as trigeminal neuralgia is concerned. In addition, we would be inclined to link up also other forms of typical neuralgic pain with the "syndrome thalamique" although for the present time there is no proof of this point.

What is the mechanism of this central pain? Three theories are prevalent concerning the origin of thalamic pain. The oldest assumes that the lesion acts as a constant stimulus upon the pain-conveying elements in the optic thalamus. Head and Holmes [3], on the other hand, believed in the liberation of the thalamic pain apparatus by interruption of an inhibitory descending cortico-thalamic tract. A third theory, finally, is based on clinical experiences in lesions of Goll's and Burdach's tracts. The posterior columns convey what Foerster calls the "perceptive epicritic" system of sensibility, the neosensibility of Brouwer, comprising the kinesthetic, pressure and discriminating sense. Foerster [2] advanced the idea that with the destruction of these tracts the "affective" system in the anterolateral columns, the palæosensibility of Brouwer, became hypersensitive.

Foerster's hypothesis was confirmed by our experience. Spinal anæsthesia involving both the palæo- and neo-sensibility increased the pain in the anæsthetized area.

Interruption of the ipsilateral pain and temperature fibres by cordotomy relieved the pain due to a lesion in the region of the optic thalamus. Subsequent cordotomy of the opposite side improved the result. The pathologic-anatomical condition within the thalamus was, of course, not changed by either operation. What was changed was the afflux of peripheral pain and temperature stimuli. We have no proof that all pain fibres were destroyed. Foerster and others claim that a system of short internuncial fibres convey pain sensations in addition to the anterolateral tracts. However, the amount of afferent painful stimuli was definitely reduced. This experience supports the conception that in the presence of a thalamic lesion peripheral stimuli—possibly subliminal under normal conditions—become supraliminal and even painful. In other words, peripheral stimuli seem to be indispensable to produce central pain. Such peripheral stimuli seem for the most part to come from the portion of the body whose central representation is involved in the thalamic lesions. However, the convergence of all sensory stimuli (probably from both sides of the body) on each optic thalamus provides the possibility of stimulation of any part of the body acting as a trigger mechanism for the pain. Consequently surgical interruption of the peripheral pathways from the painful extremities might still be followed by pain projected to this area. The theory that a continuous stimulation of the thalamic pain apparatus by a local process is essential should therefore be abandoned.

The sensory system—similar to the motor system—seems to follow the pattern of a brake machine. The activity of a lower circuit is always braked or regulated by a higher level. When this brake becomes loose, the phylogenetically older, lower system grows overactive. In the motor system this means increased motor reflex irritability; in the sensory arc increased sensitivity. The disorganization of the thalamic switchboard may further lead to an increase of the refractory period—to abnormal summation phenomena and to transformation of sensations (Gestaltwandel). Slight repeated touch stimuli suddenly produce very disagreeable pain or temperature sensation.

The mechanism of neuralgia pain suggests that a certain grade of excitation is required to pull the trigger of the paroxysm. We know to-day that the strength of a stimulus depends exclusively on the number of nerve fibres involved. Certainly not all fibres of a nerve have to be blocked to prevent a paroxysm. How far they have to be reduced relies mainly on the absence of summation phenomena which do not exist normally, but may appear with a thalamic lesion.

Clinical evidence suggests that a certain relation exists between the extent of the thalamic lesion and the number of afferent fibres which have to be interrupted to give full relief of pain. It is a common experience in retrogasserian neurotomy that in one patient pain subsides completely, although a considerable number of pain points are still demonstrable. In another patient a few omitted fibres may maintain severe pain in one or more divisions of the 5th nerve. The phenomenon of radiation of pain from one division of the trigeminal into the next may be part of the same problem.

In stressing the quantitative factor the importance of the exact situation of the lesion within the thalamus or in the thalamo-cortical system should not be neglected. It is well known that most of the smaller thalamic hæmorrhages leave the face free of pain. The trigeminal fibres end in a separate thalamic nucleus and do not become involved in the thalamic syndrome until the lesion is comparatively extensive. On the other hand, a growing granuloma of the optic thalamus may for a considerable time simulate a simple trigeminal neuralgia until gradually the pain encroaches upon the extremities (C. Winkler [7]).

These considerations first of all bear on the spinal pain system with the optic thalamus as the regulating centre. Whether the release of the thalamus itself through the lesion of the superimposed striatum and of the cortical sensory centres yields a similar syndrome, as Head and Holmes suggested, or wherein it varies, is still open to discussion.

In conclusion, we gather from our observation (1) that thalamic pain is the result of two factors: (*a*) a lesion of the pain-damping system of the posterior spinal tracts within the optic thalamus, and of such mechanisms as prevent summation, amalgamation, after-effects, &c.; (*b*) continuous slight stimulation of the peripheral pain, &c., fibres. (2) Trigeminal neuralgia, and eventually other forms of typical neuralgia, seem to represent special forms of the thalamic syndrome in which the lesions are confined either to the end places of the trigeminal system or to the thalamic sensory arrangement of an extremity, &c. (3) Sufficiently extensive surgical interruption of the pain, and other fibres in the antero-lateral columns, leaving intact posterior roots, horns and tracts, eventually supplemented by blocking of the 5th nerve, seems to be a method of relieving these unbearable and up to now incurable central pains.

REFERENCES.

[1] BROWN-SÉQUARD, C. E. "Lectures on the Physiology and Pathology of the Central Nervous System," Philadelphia, 1860, p. 19.

[2] FOERSTER, O. "Leitungsbahnen des Schmerzgefuehls," Berlin, 1927, p. 128.

[3] HEAD, H., and HOLMES, G. "Sensory Disturbances from Cerebral Lesions," *Brain*, 1911, **34**, 102.

[4] HENLE, F. G. J. "Handb. d. rat. Patholog.," Braunschweig, 1853, **2**, 131.

[5] LEWY, F. H., and FRAZIER, C. H. "The Disturbances of the Time Relation to Sensitivity in Major Trigeminal Neuralgia," *Proc. Assoc. Res. Nerv. and Ment. Dis.*, 1934, **15**, 497.

[6] WEXBERG, E. "Handb. d. Neurologie," Berlin, 1935, **9**, 192.

[7] WINKLER, C. "De Bouw van het Zenuwstelsel," Haarlem, 1920, **2**, 102.

COMPRESSION OF THE SPINAL CORD IN THE NEIGHBOURHOOD OF THE FORAMEN MAGNUM.

BY C. P. SYMONDS AND S. P. MEADOWS.

WITH A NOTE ON THE SURGICAL APPROACH,
BY JULIAN TAYLOR.

THE clinical picture which results from compression of the spinal cord at, or near, the level of the foramen magnum is not always easy of recognition. In particular the distinction from intramedullary disease (tumour or syringomyelia) may be difficult. Of the seven cases which we have to report, in one the compression was caused by an aneurysm of the right vertebral artery, in one by an atlanto-axial dislocation (probably of congenital origin) and in each of the other five by a benign tumour (endothelioma or neurofibroma). In all these cases the differential diagnosis from intramedullary tumour was for some time in doubt, and in only two instances was the correct diagnosis confidently made before operation. Three of the tumours were successfully removed by Mr. Julian Taylor with complete recovery.

There are on record many reports of comparable cases. In most of them, however, the clinical notes are incomplete, especially those which refer to the subjective and objective disturbances of sensation. Many writers have emphasized points of importance or interest in the clinical picture, but few have reviewed it as a whole.

The most important contributions to the subject which we have found are those of Elsberg [2], and Elsberg and Strauss [4]. Elsberg [2], in his monograph on spinal cord tumours, reported two cases of compression at the level in which we are interested, one from a dermoid cyst, the other from an aneurysm of the right vertebral artery. In reviewing cases of compression at a high cervical level—between the first and third segments—he laid stress upon the following points: Pain in the neck and occipital region is an important symptom and is increased on movement of the head. The patient is, therefore, apt to hold his head stiffly. Weakness first appears in the ipsilateral upper limb and is soon followed by subjective and objective sensory disturbances in the same limb. As weakness appears in the other limbs it usually does so in a regular sequence, first affecting the ipsilateral lower limb, then the contralateral lower limb, and finally the contralateral upper limb.

Elsberg and Strauss [4] again emphasize the importance of pain and rigidity in the neck, and observe as a striking feature the occurrence of dissociation in the cutaneous sensory loss of syringomyelic type. They add that the complaint of cold in one or both lower limbs, usually in the contralateral limb, is a common subjective symptom, which they have only encountered in these high cervical tumours. They note also the occurrence of atrophy in the muscles of forearm and hand in cases of extramedullary tumour confined to the upper three cervical segments.

Most of these points are illustrated in the reports which we present.

Case 1.—*Endothelioma (psammoma), on the right lateral aspect of the cord extending above and below the foramen magnum.*

W. E., female, aged 57, came to one of us (C. P. S.) on March 5, 1934, on account of weakness in her right arm and leg. Her personal history contained the story of a doubtful pulmonary tuberculosis at the left apex, and an accident in 1929, when she was concussed and unconscious for over an hour, and afterwards she suffered from headaches for several months. The history of her present illness began in 1928, when she began to have an aching pain in the right suboccipital region. This persisted until June, 1933, when she became aware of a sensation of numbness over the same area.

In August, 1933, she noticed numbness in the thumb, middle and ring fingers of the right hand. This was soon followed by weakness of the right hand, and later of the whole right arm. At this time she noticed a hypersensitiveness in her right limbs. "Sometimes when I cut my finger nails on the right hand it's an intolerable stimulus: I feel I must draw away: there is the same sort of feeling in the right leg." About the same time the right leg began to drag and she was apt to trip on uneven ground. In February, 1934, the right suboccipital pain returned, and was aggravated by coughing or jolting. A feeling of stiffness in the neck developed together with a sensation of coldness along the ulnar border of the left arm and hand.

On examination she appeared in good general health and was an excellent witness.

Cranial nerves.—The left pupil was smaller than the right, and the palpebral fissure was narrower on the left than on the right (i.e. slight left cervical sympathetic palsy). The tongue was protruded slightly to the right, but there was no wasting or fibrillation. The functions of the other cranial nerves were normal.

Motor system.—There was a spastic right hemiparesis of moderate degree considerably worse in the upper limb than in the lower, and slight wasting of the dorsal interossei of the right hand.

Sensation.—Pain and temperature sensibility was impaired over the left half of the body up to the second cervical segment. Pain was also much impaired over the upper cervical segments on the right side (fig. 1). Tactile sensibility was normal, even light stimuli being appreciated. There was no disturbance of vibration or postural sensibility.

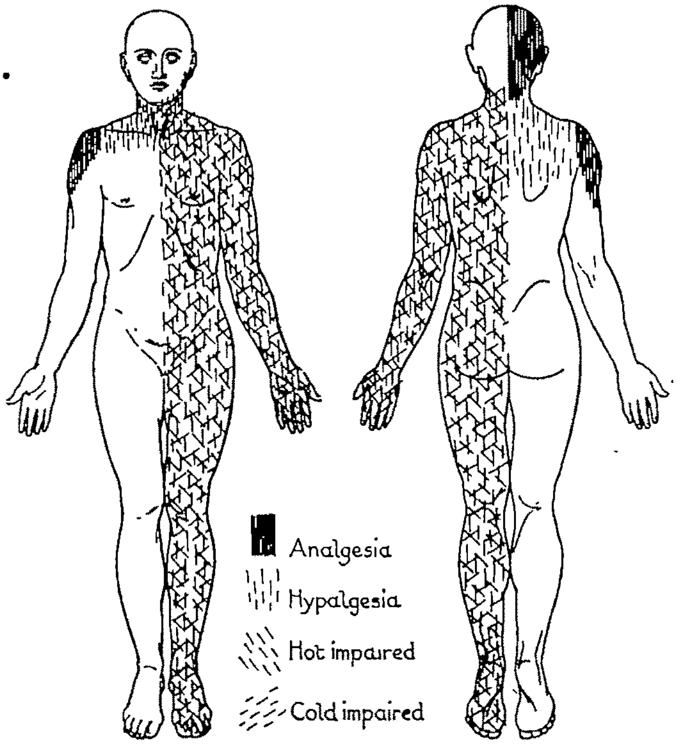

FIG. 1.—The sensory loss in Case 1.

Reflexes.—The tendon reflexes were increased in the right upper and lower extremities, the right abdominal reflexes were diminished, and both plantar responses were extensor. There was no disturbance of sphincter control. There was a slight dragging of the right leg in walking.

Spine.—There was a slight tenderness on pressure over the upper cervical spine, but no deformity. Movements of the cervical spine were unrestricted, except that rotation of the head to the left resulted in pain in the right side of the neck posteriorly.

Spinal fluid.—Lumbar puncture was performed on two occasions, in March and April, 1934. There was a quick and good rise in the cerebrospinal fluid pressure on unilateral jugular compression on each occasion, and no evidence of spinal block. The initial pressure was 155 mm. of cerebrospinal fluid which rose quickly to 270 mm. on right jugular compression, and fell quickly to 150 mm. on release of compression. The final pressure after removal of 5 c.c. was 105 mm. The cerebrospinal fluid contained one cell per c.mm. and 80 mg. total protein per 100 c.c. (60 mg. per cent. on the second occasion). There was no increase in globulin and the Wassermann reaction was negative.

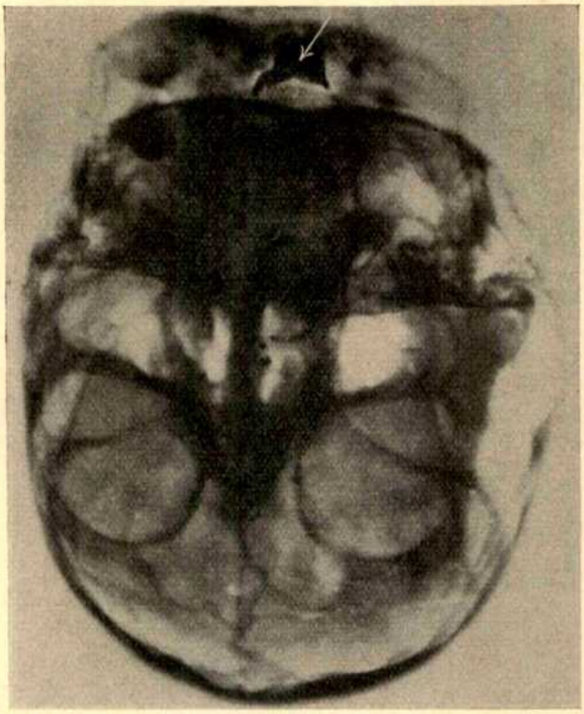

FIG. 2.—Arrest of lipiodol in Case 1. True localization. Patient head downwards.

X-ray examination.—Stereoscopic views of the cervical spine showed no abnormality.

Cisternal puncture was attempted but no fluid was obtained. The tumour was presumably near the foramen magnum and extramedullary. 1 c.c. of heavy lipiodol was injected into the lumbar sac, and an X-ray taken with the patient head downward on a tilting table, showed the lipiodol held at the level of the atlas, though a few drops had passed through into the cranial cavity (fig. 2).

Operation.—Mr. Julian Taylor operated on April 17, 1934. The plan adopted was exposure of an area centred on the foramen magnum, necessitating an upper cervical laminectomy together with a limited craniotomy. On reflection of the dura mater, the proximal cervical cord was seen to be displaced and rotated to the left by a lobulated mass lying to the right (fig. 3). The upper cervical posterior roots were seen coursing over the tumour. The roots and cord were freed from the tumour with some difficulty, and on release from these structures the tumour was found to be attached to the dura at the level of the foramen magnum. Division of this attachment enabled delivery of the tumour from its bed. The major portion of the tumour was situated in the posterior cranial fossa, while the smaller part extended down the spinal canal for a short distance.

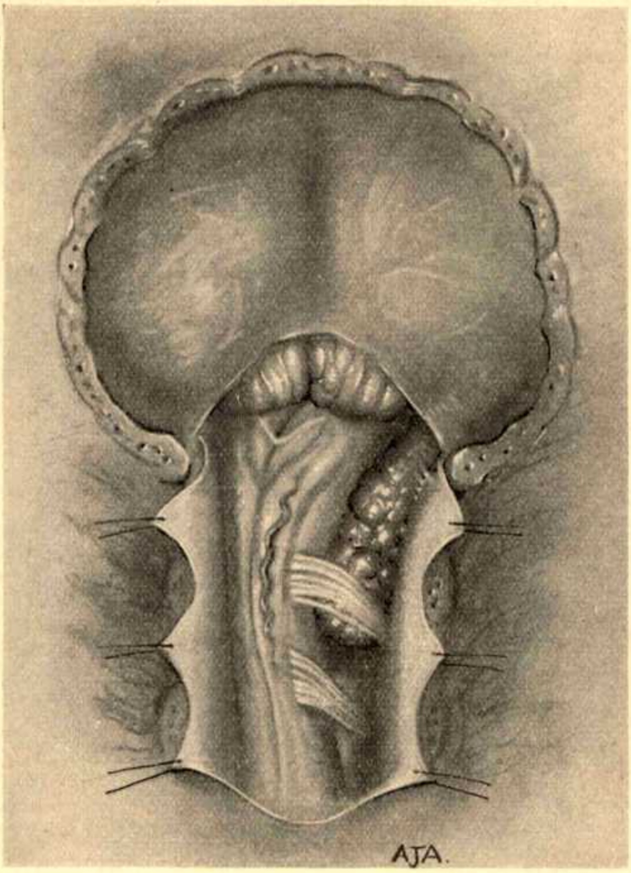

FIG. 3.—The tumour in Case 1, from a sketch made at the operation.

Histological examination.—The tumour was a whitish, encapsulated lobulated, mass weighing 7 grm. and measuring 3·5 × 2·5 × 1·5 cm. Microscopical examination proved it to be a psammoma.

Post-operative history.—There was a considerable degree of post-operative weakness of the right arm, but this was only of temporary duration, and subsequent progress was steady.

Examined on February 28, 1935, ten months after her operation, she was able to walk two miles before any sensation of fatigue appeared in her right leg. She had normal use of her upper limbs, but after writing for a long time noticed occasional spasm of her right arm—a forward movement at the shoulder, with pronation at the wrist; also occasional "jerks" in her left hand. She was unable to distinguish between hot and cold water with her left lower limb, but could do so with the left upper limb. Elsewhere sensation appeared to her normal save for a constant feeling of coldness along the medial border of the left upper limb.

There was no trace of cervical sympathetic weakness. The right trapezius was weak and wasted and there was some limitation of passive movement at the right shoulder. There was slight weakness and spasticity of the right upper and lower limbs. Sensory examination showed an area of cutaneous analgesia roughly corresponding with the 4th and 5th cervical segments on the right. On the left there was loss of sensation to pain, heat and cold over the lower limb and trunk and upper limb up to the level of the 7th cervical segments, above which responses gradually became more accurate until, above the clavicle, they were normal.

The tendon reflexes in upper and lower limbs were brisker on the right than on the left side. The right plantar response was extensor, the left flexor.

Case 2.—*Endothelioma on the right postero-lateral aspect of the cord, extending above and below the foramen magnum.*

Mrs. S., aged 50, was referred to one of us (C. P. S.) on November 1, 1933. Between one and two years before the date of examination this patient began to suffer from pains at the back of the neck and head, subsequently radiating down the right arm. This was followed by tingling, weakness and stiffness of the right arm and hand. There was also some tingling in the left hand, and finally progressive weakness of both lower limbs, more especially of the right lower limb. There was no history of paræsthesiæ in the lower limbs and no sphincter disturbances.

Cranial nerves.—The pupils were irregular but reacted normally. The cranial nerves were otherwise normal.

Motor system.—There was a spastic weakness of all four limbs, more right than left, and equal in upper and lower limbs.

Sensation.—Tactile sensation was everywhere normal. Over the left limbs and trunk there was complete analgesia up to a poorly defined level at the juncture of the 2nd and 3rd cervical segments, except over the 2nd to 5th sacral segments where sensation to pin-prick was relatively unimpaired. On the right side there was hypalgesia of similar distribution. There was impairment both to heat and cold over the left trunk and limbs of the same distribution as the analgesia. Responses both to the hot and cold tests were variable and appreciation slow. There was no loss over the right trunk or limbs.

The sense of passive movement was perfect in all digits of both feet and left hand; in the right hand there was some uncertainty of response, but no gross defect.

Appreciation of vibration was completely lost over the whole right upper limb from fingers to acromion process and clavicle, inclusive. Elsewhere appreciation was normal save over the iliac crests, but the patient being extremely stout, the last observation was considered to have no clinical importance.

Reflexes.—The triceps, biceps, supinator, knee and ankle jerks were all increased on the right side. Ankle clonus was present on the right. All abdominal reflexes were absent. The right plantar response was extensor, the left was sometimes absent, sometimes extensor. There was no impairment of sphincter control.

Gait was spastic and weak, but the patient was able to walk unaided.

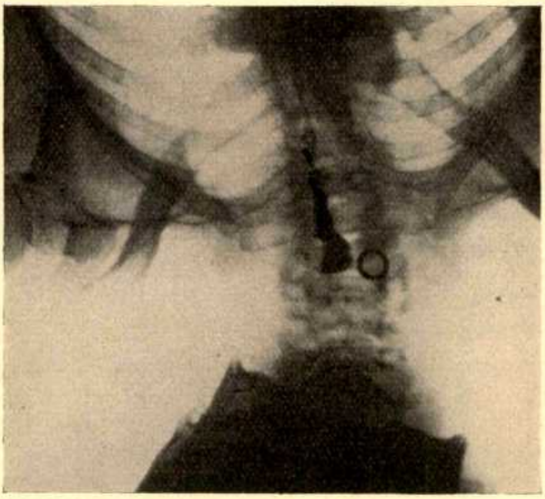

FIG. 4.—Arrest of lipiodol in Case 2. False localization. Patient head downwards.

Spine.—The patient held her neck somewhat rigidly, but was able to perform all movements on command except extreme flexion of the neck. Passive movement in this direction was also limited. The upper cervical spines were tender on pressure.

Spinal fluid.—The initial pressure was 75 mm. of water. Compression of the left jugular vein gave a rise to 170 mm.; of both jugulars, a rise to 220 mm. On each occasion both rise and fall were slow. The fluid was clear and contained no cells. The protein was 100 mg. per cent. The Wassermann reaction was negative.

X-ray examination.—Stereoscopic views of the cervical spine showed no abnormality. An attempt was made at cisternal puncture, but failed. Subsequently, 2 c.c. of lipiodol were injected by lumbar puncture. The patient was gradually tilted to an angle of 80° and the shadow of the lipiodol observed. It flowed gradually to the level of the 6th cervical vertebra, when it became arrested, and no further movement was observed at the end of ten minutes (fig. 4).

Operation.—Mr. Julian Taylor operated on December 12, 1933. The spinal cord was exposed by removal of the 3rd to the 6th laminæ. No abnormality was observed. The exploration was carried higher by the removal of the arches of axis and atlas, and the tumour was then discovered lying upon the right postero-lateral surface of the cord just below the foramen magnum, and extending upwards to a point just below the skull. It was entirely removed piecemeal.

Histological examination.—Dr. Greenfield reported the tumour to be a cellular endothelioma with large whorls of fleshy cells centred on a small knot of hyalinized connective tissue often partially calcified.

Post-operative history.—No complete examination was made until five weeks after operation. The patient was sensitive and resented disturbance. There was no loss of sphincter control in the post-operative phase, nor any trigeminal anæsthesia or nystagmus. Motor and sensory function in the right upper limb showed improvement within the first week.

On January 20, 1934, there was no abnormality of the cranial nerves.

Weakness and spasticity were apparent in all four limbs. Weakness was greater on the right than the left, and most evident in the small muscles of the right hand, and extension of right wrist and elbow. In addition there was definite wasting of the small muscles of the right hand.

Pin-prick was appreciated normally and equally in both lower limbs and also over the trunk up to about the 4th thoracic segment. Above this up to the clavicle, there was relative analgesia on the left, and above this again a zone of intense over-reaction with raised threshold up to and including the second cervical segment. No defect of postural or vibration senses could be discovered in any part. The reflexes showed no important change from before operation. The patient walked quite well unsupported.

She attended by request for examination by one of us (S. P. M.) on December 4, 1935, that is, nearly two years after the operation. She did not complain of any disabilities. She was able to walk well and perform her ordinary household duties which included cooking. She had, however, aching pains at the back of the head and neck and in the right shoulder.

On examination there was no defect of the cranial nerve functions; no defect of sensation to touch, pin-prick, heat, cold, postural tests or vibration, in trunk or limbs; no weakness, wasting or dystonia. The tendon-jerks in upper and lower limbs were brisk and equal, all abdominal reflexes present and equal, plantar responses both flexor, though left not so easily obtained as right. Sphincter control and gait were normal.

Case 3.—Endothelioma on the right antero-lateral aspect of the cord extending above and below the foramen magnum.

Mrs. H. L. B., aged 42, was referred to one of us (C. P. S.) on October 25, 1935, on account of weakness and numbness in her limbs. Her family and personal history contained nothing relevant. She had been married sixteen years, but there had been no pregnancy. The story of the present illness began two years previously, when she noticed that whenever she was in "a tight jam" (e.g., if she was driving in a car and had a narrow escape from accident) a momentary tingling sensation would run up her right arm from fingers to shoulder. At about the same time she began to experience occasional shooting pains at the back of her head on the right side, which were ascribed to neuritis. As time progressed the right hand became progressively more dead and useless. The pain at the back of the head recurred and spread across her neck and shoulders, first on the right side and then on the left. During the past month she had noticed a numbness in the left little finger which spread radially to the other digits. Later the numbness spread down the left side of her body and involved the left lower limb, in which it was associated with a pain "like sciatica." At the same time both lower limbs became weak.

On examination she proved an intelligent and co-operative patient.

Cranial nerves.—These showed no abnormality, save for a slight right-sided enophthalmos. There was no nystagmus, no impairment of sensation in the right trigeminal field, and no weakness of right sterno-mastoid or trapezius.

Motor system.—In the upper limbs there was a severe degree of weakness with moderate spasticity, greater in the right than the left. Both lower limbs were slightly weak and spastic, the right again being more affected than the left. No clonus was obtained at wrists, fingers or ankles.

Sensation.—There was no gross defect to light contact, but over the left trunk and limbs, from the second cervical segment downwards, occasional stimuli were missed by contrast with uniformly correct appreciation on the right.

Pin-prick over the 2nd to 4th cervical segments on the right was less vividly appreciated than over the remainder of that side of the body. On the left side there was complete analgesia below the trigeminal field, with the exception that within an area corresponding with the 6th to the 11th thoracic segments the prick was occasionally felt, and, if felt, was associated with marked flinching and an exclamation of pain. At one examination islands of relatively normal sensibility were found in the lower sacral segments. The upper level of cutaneous analgesia at its boundary with the trigeminal field was very sharply defined.

Over the 2nd to 4th cervical segments on the right, heat and cold were less vividly appreciated than on the rest of that side of the body.

On the left there was loss of all sensation to heat and cold below the trigeminal field down to and including the 5th thoracic segment. Below this, in a zone covered by the 6th to 11th thoracic segment an anomalous state existed. There was no recognition of heat, even if of painful degree. The cold tube, however, was invariably called hot with flinching and an exclamation of pain. Below this again, from the 12th thoracic to 1st sacral segments, there was loss of all sensation to both heat and cold. Over the remaining sacral segments heat was appreciated as such, whereas the cold tube was called warm.

The sense of passive movements was completely lost in all digits of both hands. In the left toes the slightest movements were immediately and correctly appreciated. In the right toes small movements were slowly, but usually correctly, appreciated: with larger movements there was no difficulty.

Vibration sense was completely lost over the trunk and upper limbs, including the clavicles and iliac crests. In the lower limbs it was lost on the right, but present on the left when the tuning fork was applied to internal and external malleoli, tibia and patella.

Reflexes.—The triceps, biceps and supinator jerks were abnormally brisk, more so on the right than the left. The abdominal reflexes were absent. The knee and ankle jerks were brisk, the right more so than the left, Both plantar responses were extensor. A pin dragged across the skin over the left anterior thoracic wall at the level of the axilli provoked a reflex spasm of the corresponding upper limb, comprising adduction at the shoulder, flexion at the elbow, and pronation and flexion at the wrist. No such reflex was present on the right. There was no disturbance of sphincter control.

Gait was spastic and unsteady, but the disability was much less in the lower than in the upper limbs.

Spine.—Voluntary movements of the head and neck were carried out to command without absolute restriction, but the patient preferred to turn head and trunk together in rotation, especially when rotating to the right. Passive movements were unrestricted, save that full rotation, especially to the right, gave rise to an uncomfortable sensation of tightness, referred on each occasion to both sides of the neck and the back of the head.

No tenderness of the cervical spines could be detected on palpation.

Spinal fluid.—The initial pressure was 40 mm. of water (about ½ c.c. was lost on account of a sticking tap before the pressure reading was taken). Compression of the left jugular vein gave no rise of pressure. Compression of the right jugular gave a slow rise to 80 with a more rapid fall on release. Compression of both jugulars gave the same result as compression of the right alone. All observations were repeated. The residual pressure after the removal of 5 c.c. of fluid was 5 mm. of water. Examination of the fluid (Dr. J. G. Greenfield) showed it to be clear and colourless. It contained 2·5 cells per c.mm., small and medium mononuclears: total protein was 200 mgm. per cent.: Nonne-Apelt and Pandy tests were positive: gold sol. 0000122110: Wassermann reaction was negative.

X-ray examinations.—Stereoscopic views of the cervical spine showed no abnormality. On the third day after the initial lumbar puncture 2·5 c.c. of lipiodol were injected by lumbar puncture. The patient was then tilted to an angle of 20° from the vertical plane head downwards and the shadow of the lipiodol observed. It was seen at the site of injection, gradually becoming elongated, but showed no movement at the end of several minutes.

Operation.—Mr. Julian Taylor operated on November 4, 1935. At the level of the foramen magnum the posterior aspect of the cord appeared pale and slightly swollen. The apparent swelling proved to be due to slight backward displacement by a tough encapsuled tumour lying upon the right anterolateral surface of the cord in close proximity to the emerging fibres of the spinal accessory nerve. The tumour was completely removed at the end of an operation lasting two hours.

Histological examination (Dr. J. G. Greenfield).—A firm, rather brown, tumour, roughly pyriform in shape and weighing 6 grm. Histologically the tumour is an endothelioma composed of fairly fleshy cells in small whorls and larger masses which are separated by very thick trabeculæ of collagen, in which the vessels run. Although in many places collagen preponderates over tumour tissue, there is no tendency to the formation of hyaline knots in the centres of the whorls:

Post-operative history.—The patient made a good recovery from the effects of the operation with no disturbance of sphincter control. On November 12 her general condition was good and allowed of a fairly full examination (S. P. M.). As a result of the operation, new physical signs had developed as follows: Cervical sympathetic weakness on the right was more evident, i.e. ptosis and miosis in addition to enophthalmos. Nystagmus was present on deviation of the eyes in either direction in the horizontal plane, being more marked and coarser to the left. There was also an irregular fine nystagmus on upward deviation. The right corneal reflex was abolished, the left remaining brisk. There was analgesia over the whole right trigeminal field, the loss affecting all divisions equally and being strictly confined to the parts supplied by the 5th nerve. There was no loss of sensation to cotton-wool. The motor functions of right trigeminal were unaffected. There was paralysis of right sterno-mastoid and trapezius. The other cranial nerves were unaffected.

The cutaneous sensory loss over trunk and limbs remained unchanged. There was no loss of sensation to cotton-wool. Posterior column function already showed improvement; postural sense was grossly impaired in the right fingers, moderately so in the left, slightly impaired in the right toes, normal in the left. Appreciation of vibration was much impaired below the right elbow, but not as much impaired as might have been expected from the degree of postural loss. Over the left upper limb vibration was normally appreciated. The disturbance of motor function in the limbs and of the deep and superficial reflexes remained as before operation.

On November 30 a more complete examination was possible (C. P. S.). The patient now complained that when she was tired reading was difficult, but became easier if she closed one eye. No diplopia could be elicited. Nystagmus was now evoked only on deviation to the left, and was more marked in the left eye. The cranial nerves otherwise showed no change. Over the left trunk and limbs pin-prick was appreciated as such, but was said to be less sharp than on the right and there was no flinching reaction. To the hot and cold tubes over the same distribution the response as a rule was, "I'm not sure"; sometimes, "Hot [or cold] I think," and then generally correct. Over a zone conforming to the left 6th to 11th thoracic segments, although heat and cold were not distinguished, at contact with the cold tube she flinched and said, "It makes me jump." She was unable to explain this sensation further. This response was invariable. There was no sensation of pain or flinching to pin-prick in this zone. The functions of the posterior columns showed further improvement; postural sense was normal in both lower limbs and in the left upper limb. In the right upper limb the following observations were made:—

Fingers and wrist: response slower than on the left with a good many mistakes.

Elbow: Response much slower than on the left, occasionally correct, but more often "not sure."

Shoulder: Grossly defective. ("I can't tell at all.")

Vibration was well and equally appreciated on the two sides of the body on the dorsa of the feet, tibiæ, iliac crests, lower costal margins, fingers (all digits separately), wrists, elbows and clavicles. On the right acromion process, however, vibration was constantly less well appreciated than on the left; at a low range of excursion of the tuning fork vibration was not felt on the right ("only heard"), but normally appreciated on the left.

There was a great improvement of motor function. The right upper limb was slightly spastic and generally weak, but there was no marked degree of weakness except at the shoulder and in the hand. These was slight spasticity of the right lower limb and a just appreciable weakness of all flexor movements as compared with the left.

At this stage, however, a new symptom had appeared in the shape of wasting in the intrinsic muscles of the right hand. The thenar eminence was flattened and, with the hand lying palm upwards, the thumb fell back into line with the fingers. The interosseous spaces on the back of the hand showed as deep furrows. There was the beginning of a *main en griffe*. All movements were correspondingly weak. The deep and superficial reflexes showed no important change.

On January 6, 1936, the patient was again examined (C. P. S.). She had now been on her feet for a month and was able to do most things with her hands, the right being still the stronger. She was able to write without much difficulty. Her only complaints were that she still had difficulty with vision, having to close one eye for detailed work, and that on waking in the morning she felt giddy and sick, and, if she took a solid breakfast, often vomited.

The cervical sympathetic palsy, nystagmus and sensory loss over right face were present as before. The right corneal reflex was present and equal with the left. The right sternomastoid and trapezius, though weak, were contracting well.

The cutaneous sensory defect on the left had altered slightly. Its upper limit had receded and was less well defined. Analgesia was complete up to and including the 7th cervical segment. Above this it was incomplete and shaded off gradually to normal sensation at the upper level of the 3rd cervical segment. The loss to heat and cold was complete up to and including the 5th cervical segment and shaded off to normal at the level of 3rd cervical segment.

On this occasion, over the areas where discrimination between heat and cold was lost, the patient showed a tendency whenever she guessed to call all stimuli "warm." The zone of flinching to cold between the 6th and 11th thoracic segments remained as before.

There was nowhere any defect of postural or vibration sense. Wasting and weakness of the right hand were still evident, though improved. Apart from this, there was little weakness anywhere, though all four limbs were a little spastic, more so on the right than the left.

All the tendon-jerks were brisk, those of the upper limbs exceptionally so, but there was equality between the two sides. The abdominal reflexes were absent on the right, present on the left; the right plantar response extensor, the left flexor.

In walking, the patient showed an inclination of occiput to right shoulder, and tended to circumduct the right lower limb.

Case 4.—Neurofibroma on the anterior aspect of the cord mainly below the foramen magnum, but with a small protusion through and above it.

Mrs. C. N., aged 38, was admitted to the National Hospital, Queen Square, on August 3, 1934, under the care of Dr. James Collier, and was examined by one of us (S. P. M.).

The patient was one of fifteen children, of whom six were living at the time of the patient's admission to hospital. She had been married seventeen years, and had six healthy children, including one set of twins. She had been a strong healthy woman until the onset of the present illness.

Symptoms commenced in 1930, four years previous to admission to hospital, when the patient was pregnant. She then noticed a feeling of numbness and tingling in the right hand which slowly became weak. She also had œdema of the legs at this time, but was told that this would clear up after the confinement. The numbness slowly spread from the right hand up to the elbow, but no further.

In 1932, two years before admission, weakness and dragging of the right leg became manifest. Following this her neck became weak, so that her head fell forwards, and maintenance of the erect attitude was impossible. The right arm and leg and the neck became progressively weaker.

Early in 1933 she was admitted to a hospital for a month, and at this time the weakness of her neck improved and she could walk with a slight limp. In November, 1933, nine months before admission, she became progressively worse, and her neck, right arm and right leg were much weaker. Four months previous to admission the left leg also became weak, and finally the weakness extended to the left arm. She was by this time unable to feed herself, and had difficulty in breathing, coughing and sneezing. There was no difficulty in speaking and her voice remained unchanged. Nor had there been any dysphagia.

There had been little pain, though she had considerable "soreness" of the back of her head during the latter few months, and her head felt tight, "as if in a vice." Turning the head produced pain in the neck, more particularly if she turned her face to the right. She stated that she was still able to feel in the paralysed limbs, and could still appreciate touch or the warmth of a hot bottle. Her legs and feet were always cold.

There had been no disturbance of micturition, but she had been subject to constipation for a few months since being confined to bed.

On examination in August, 1934, the patient lay on her side, with her head slightly extended to assist respiration. There was marked respiratory distress, the respiratory rate being 30 per minute. She was breathing almost solely with the sternomastoids and platysma, and could only talk in gasps.

Cranial nerves.—The right palpebral fissure was smaller than the left, and on one occasion there was a fine quick horizontal nystagmus on lateral deviation. The cranial nerves showed no other abnormality.

Motor system.—There was a severe degree of weakness in all four limbs with moderate spasticity. The upper limbs were equally weak, but the left lower limb was weaker than the right. There was generalized muscular wasting of both upper limbs.

The neck and trunk musculature was also very weak. Both sternomastoids contracted during respiration, but both were weak on active rotation of the head. The patient was unable to lift the head from the pillow. Extension of the neck was feeble, but slightly stronger than flexion. She was able to hold the head erect if she was supported in a sitting position. The patient was unable to sit up without assistance, and the abdominal musculature was very flaccid, but contracted feebly on coughing or straining. The intercostal muscles were paralysed and the epigastrium retracted on inspiration, suggesting diaphragmatic paralysis.

Sensation.—Owing to her general state, the patient was a poor witness. On admission there was a band of impairment to pin-prick on the right side from the 1st dorsal to the 1st lumbar root areas. Vibration was lost in the left lower limb, and there was loss of postural sense in both lower limbs.

Later examination revealed a sensory level to pin-prick at the junction of the 2nd cervical and trigeminal sensory areas in the right side, with impairment of pin-prick over the left side of the body up to the neck.

Tactile sensibility, tested with cotton-wool, was very little affected.

The appreciation of vibration was much impaired in all four limbs, and in the trunk up to the cervical spine. The sense of passive movements was lost in the fingers of both hands and in both great toes.

Reflexes.—The arm jerks, knee jerks and ankle jerks were exaggerated in all four limbs, and there was knee and ankle clonus. The abdominal reflexes were absent, and both plantar responses were extensor. There was no disturbance of sphincter control.

Spine.—The spine of the axis was very tender on pressure, and there was much pain in this region when the head was moved from side to side. There was no deformity of the cervical spine.

Spinal fluid.—Lumbar puncture showed an initial cerebrospinal fluid pressure of 128 mm. of water, rising to 148 mm. on right jugular compression. There was a steady, but not quick, rise on bilateral jugular compression to 210 mm., and a more rapid fall to the initial pressure on release. After removal of 5 c.c. of fluid, the pressure fell to 20 mm., rising to 48 mm., when bilateral jugular compression was repeated.

Examination of the cerebrospinal fluid (Dr. J. G. Greenfield) showed it to be clear and colourless, with 5·5 cells per c.mm : total protein 200 mg. per cent. ; Nonne-Apelt and Pandy tests strongly positive; gold sol, 0000012100; Wassermann reaction was negative.

X-ray examination.—Lateral and anteroposterior X-rays of the cervical spine showed no abnormality.

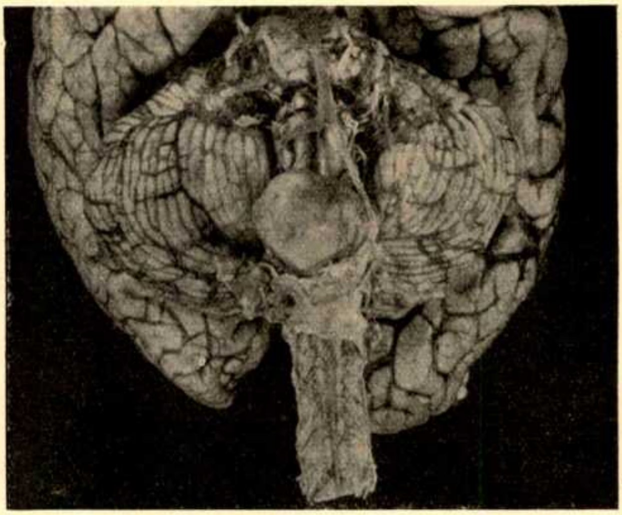

FIG. 5.—The tumour in Case 4.

Through the kindness of Dr. Collier we were able to examine the patient together and were of opinion that the case was one of extramedullary tumour just below or at the level of the foramen magnum.

Operation.—Mr. Julian Taylor operated on September 4, 1934. The exposure described in Case 1 was made, but the appearances on opening the dura were very different. The lower part of the medulla and upper part of the spinal cord presented what appeared to be three spheroidal prominences, giving the impression of some intramedullary change, possibly with cyst formation. On account of the precarious state of the patient, together with respiratory difficulty, it was considered unjustifiable to divide the nerve roots in order to facilitate exposure of the front of the cord, especially as the appearances described seemed to be indicative of the pressure of an intramedullary tumour. Further intervention being deemed inadvisable the wound was closed.

The patient died later in the same day. Post-mortem examination (Dr. J. N. Cumings) revealed a large tumour lying anterior to the medulla, part of which was extruded through the dura, forming a dumb-bell tumour (fig. 5). It was about 1 in. long and ¾ in. wide and felt moderately soft. A small portion, about a third of the tumour, protruded through the foramen magnum, which had been enlarged. The first three cervical segments appeared a little larger than usual.

Histological examination (Dr. J. G. Greenfield).—The tumour is oval, smooth and fleshy. It is a neurofibroma with many beautiful palisaded whorls. The main part of the tumour is fleshy with oat-shaped cells. The nuclei vary considerably in size, but all are rather vesicular in type. There is considerably more collagen in the whorled palisade areas than elsewhere.

Case 5.—Separation of the odontoid process with compression of the cord.

D. A., male, aged 47, labourer, was referred to one of us with the complaint of weakness of the right arm and leg, and subsequently admitted to the National Hospital, Queen Square. In his past history the only episode of possible relevance was an accident two years previously. He was struck by a running trolley on the back of the right shoulder and arm, was off work for a week, and on light work for several months. Eighteen months before admission he noticed weakness in the right forearm and hand. At about the same time he began to have a dull aching pain in the depth of the forearm, and an occasional prickly numbness along the medial side of the hand and medial three fingers. These symptoms became progressively worse until, at the end of six months, the weakness of his arm caused him to leave his work. Shortly after this, his right leg began to drag in walking. For a year he had had difficulty in starting micturition, and was unable to control a loose motion.

For three months he had complained of pain in the back of the neck and head. This was described as a shell of pain clapped on to his head and was aggravated by stooping.

On examination the cranial nerves showed no abnormality.

Motor system.—The upper limbs presented a moderate degree of spasticity, considerably greater in the right than in the left. Associated with this was weakness of upper neuron type, severe in the right limb, especially in dorsiflexion of the wrist, slight in the left. Both lower limbs were a little spastic, and there was slight weakness of the right limb in movements of flexion.

Sensation.—There was no gross defect of tactile sensation, but over the 2nd to 4th cervical segments light stimuli were occasionally missed. Over the 2nd to 4th cervical segments on both sides sensation to pin-prick was impaired. There was imperfect discrimination of heat from cold over the whole of the left trunk and limbs from the 2nd cervical segment downwards.

The sense of passive movement was defective in the right thumb, elsewhere normal. The appreciation of vibration was completely lost over right trunk and limbs up to and including the acromium process. On the left it was lost in the lower limb up to and including the iliac crest, but was appreciated over the trunk and upper limb.

Reflexes.—The triceps, biceps and supinator jerks on both sides were very brisk. A scratch with a pin anywhere within the territory of the 4th cervical to 6th thoracic segments provoked a strong reflex movement in the upper limb of the same side taking the form of flexion at the elbow and slight abduction at the shoulder. The abdominal reflexes were absent. The knee-jerk on both sides was very brisk: the right ankle-jerk brisker than the left. Patellar clonus was present on both sides, ankle clonus on the right. Both plantar responses were extensor. There was difficulty in starting micturition, and imperfect control of defæcation after a purge.

Walking was quick, but with apparent effort, and slight dragging of the right leg.

Spine.—The 2nd cervical spine was unduly prominent and a little tender on pressure. There was no limitation of movement or rigidity in the neck.

Spinal fluid.—The initial pressure was 85 mm. of water. Right jugular compression gave a prompt rise to 230 with prompt fall on release. Left jugular compression gave the same results. The residual pressure after removal of 5 c.c. was 45 mm.

Examination of the fluid (Dr. Greenfield) showed it to be clear and colourless. It contained 1 cell per c.mm; total protein 35 mg. per cent.; Nonne-Apelt and Pandy tests were negative; gold sol no change; Wassermann reaction negative.

X-ray examination of the cervical spine showed no abnormality. 2 c.c. of lipiodol was injected intrathecally in the lumbar region and the patient examined on the tilting table. When the patient was tilted head downwards the flow of the lipiodol was very slow. Eventually the greater part of it was arrested at the level of the upper border of the 5th cervical vertebra, but some passed on and entered the skull.

Operation.—Mr. Julian Taylor operated on January 29, 1935. When the cord was exposed it was seen to be pushed rather acutely backwards at the level of the junction between atlas and axis, and a bony projection into the spinal canal was felt at this level. This was thought at the time to be an ossified chondroma, for it was very hard and could not be incised. The patient died from respiratory failure within forty-eight hours from the time of operation

Post-mortem (Dr. Greenfield).—The cord was found to be curved sharply backwards (concavity forwards) at the level of the body of the axis. The head was unduly movable on the neck between the atlas and the axis and it was clear that the odontoid process of the axis was not attached to its body, the only connection between the body of the axis and the vertebra above it being two fibrous strands which were stretched to about a quarter of an inch in length. The upper surface of the body of the axis was rounded in conformity with its articular surfaces which were very large. The atlas vertebra was normal and contained in its ring the odontoid process of the axis, which had an anterior articular facet, corresponding with a facet on the back of the anterior ring of the atlas, and a plate of fibro-cartilage on its lower surface. Professor T. B. Johnstone, who examined the specimen, considered the abnormality to be of congenital origin. The cord at this level was definitely compressed and thinned.

Case 6.—*Aneurysm of the right vertebral artery.*

R. F., electrician, aged 49, was admitted to the National Hospital, Queen Square, under the care of one of us (C. P. S.) on November 28, 1935, complaining of numbness and weakness of the right arm and dragging of the right leg.

There was nothing relevant in his family or past history.

The first symptom which might be connected with his present illness was a bout of hiccoughing eighteen months before admission, which had lasted on and off for ten days and had recurred occasionally during the succeeding three months.

Fourteen months before admission he first had pain in the right shoulder and tingling in the upper arm which gradually spread to involve the whole limb, including the thumb and fingers. At about the same time he experienced occasional giddiness on exertion—for instance running for a bus. Objects would momentarily seem to revolve in a clockwise direction. After he had stood still for a moment or two the symptom would disappear. All these symptoms cleared up and he was well for five months. Three months before admission the pain in the right shoulder recurred, followed by the tingling as before. The right hand and fore-arm became numb and stiff, and six weeks before admission he was unable to hold a pen. There was also recurrence of the giddiness. Subsequently he experienced stiffness and numbness of the left hand and fingers; the numbness began in the little and ring fingers and spread slowly up the ulnar side of the fore-arm to the elbow. About the same time he noticed dragging of the right foot, and within a week found himself unable to walk without support. At this time also he noticed on walking a tight feeling around his trunk at the level of the umbilicus "as if someone had tied a rope belt" round him. Subsequently the left leg became numb and stiff and he complained of some stiffness in the neck.

Cranial nerves.—At rest there was a continuous vertical nystagmus which was evident also on lateral deviation in the eyes in either direction and on downward deviation, but absent on upward movement. This nystagmus had a range of about 1 mm. and a frequency of about 2 per sec. Associated with the vertical movement was a slight anti-clockwise element. The corneal reflex was sluggish on both sides, more so on the right. Over the right trigeminal field there was slight hypalgesia and thermohypæsthesia, rather more marked peripherally than centrally, and in the second and third divisions more than the first. On phonation the pharyngeal wall moved slightly to the left. There was slight wasting and weakness of right sternomastoid and trapezius. The right half of the tongue was wasted, and it was protruded a little to the right. Fine fibrillation was constant in its right half and occasionally in the left.

Motor System.—There was no spasticity of the upper limbs, but the right showed weakness of pyramidal type and distribution. There was also slight wasting of the muscles of the right thenar eminence and dorsal interossei.

There was clinical evidence (absent Litten's sign) of paralysis of the right half of the diaphragm, confirmed by X-ray screening. The lower limbs were not spastic, but the right was weak.

Sensation.—There was no gross defect to cotton wool, but a relative defect over the right, 2nd and part of the 3rd cervical segments, and on the left hand and fore-arm and the whole lower limb with the exception of the back of the thigh and buttock.

There was complete analgesia over the upper and outer aspects of the left upper limb (roughly the territory of 5th and 6th cervical segments) and the antero-external aspect of the left leg (roughly the territory of the 5th lumbar segment). From the analgesic areas hypalgesia extended over the whole of the left upper limb on to the neck and trunk to include the 2nd cervical segment above and the 4th thoracic below. In the lower limb hypalgesia was evident up to the 2nd lumbar and down to the 2nd sacral segments, but was less than in the upper limb.

The areas of loss and impairment to heat and cold corresponded closely with those for pain. There was no dissociation between heat and cold.

The sense of passive movement was absent in fingers, wrist, elbows and shoulders of both upper limbs, but normal in the lower limbs.

Appreciation of vibration was nowhere lost, but was markedly impaired in the right upper limb up to and including the clavicle and, by comparison with the lower limbs, impaired in the left upper limb.

Reflexes.—The triceps, biceps and supinator, knee and ankle jerks were all brisker on the right than the left. The abdominal reflexes were absent. The plantar responses were extensor. There was no defect of sphincter control. The patient could walk only with support, dragging the right leg.

Spine.—The head was carried stiffly, but there was no limitation of movement nor any tenderness or deformity of the cervical vertebræ.

Spinal fluid.—The initial pressure was 160 mm. of water, with free rise and fall on compression of either jugular vein, the heights reached being 300 mm. on compression of the right jugular, 280 mm. on compression of the left. The fluid was clear and colourless. It contained no cells and 60 mg. per cent. of protein. The gold sol showed no change. The Wassermann reaction was negative.

X-ray examination.—X-rays of the cervical spine showed no abnormality. No attempt was made at lipiodal injection.

Operation.—Mr. Julian Taylor operated on December 20, 1935 A large, rounded, oval, dark tumour mass was found lying upon the right posterolateral aspect of the medulla. The main mass was within the cranial cavity, but the lower end extended through the foramen magnum and obscured the cord down to the level of origin of the first cervical root. Attempt at removal led to severe hæmorrhage and had to be abandoned. Death ensued a few hours later. At post-mortem the tumour proved to be an aneurysm (presumably congenital) of the right vertebral artery.

Case 7.—Endothelioma on the left anterolateral aspect of the cord extending above and below the foramen magnum.

Miss T., aged 43, was referred to one of us (C. P. S.) on March 16, 1936. She complained that for the past three years she had had pain at the back of her head. This was bilateral, suboccipital, and of a throbbing character, with an occasional shooting pain radiating forward into either temple. It was always more severe at night and in the early morning, usually wearing off before 10 a.m. It was worse at her periods. In the morning there was a feeling of pressure upon her head, as if there was something loose inside it. At all times she was subject to discomfort on movement of her head, especially when bending forwards. In the past fortnight her left hand had felt cold, and she had not been able to feel things so well with it. There had also been numbness in the left thumb.

She had always been of a nervous disposition, but though she was clearly of a psychoneurotic personality there was sufficient in her story to arouse the suspicion of a high cervical tumour. A careful examination was therefore made with this suspicion in view, but no abnormal physical signs could be found.

She was next seen on December 17, 1936, when her main complaint was still of pain at the back of her head, which was aggravated by bending forward, by any physical effort, by coughing or sneezing, and especially by straining at stool. She complained also of numbness and a stinging sensation in the back of her head, and of painful stiffness in her shoulders and neck. Her hands and arms felt numb and stinging, the hands swollen and heavy. The first sensation of numbness in the right hand had appeared in October. About the same time she began to have a continuous sensation around her neck, just above the Adam's apple, as if she were wearing a tight collar. Quite recently she had had a sensation of coldness around her right knee.

Again a full examination was negative.

She was admitted to the National Hospital, Queen Square, on January 8, 1937. The Resident Medical Officer, Dr. Smyth, noted that the tendon-jerks in the upper limbs were abnormally brisk on both sides, and that full flexion of the head caused her slight pain, but could find no other abnormality. Stereoscopic X-rays of the cervical spine revealed no abnormality. Lumbar puncture on January 18, 1937, showed a pressure of 85 mm. with rises to 170 mm. on right, 150 mm. on left, and 250 mm. on bilateral jugular compression. The rise and fall of pressure on each occasion were a little slow.

The spinal fluid was slightly yellow, contained no cells, but the total protein was 1,200 mg. per cent.: Nonne-Apelt and Pandy tests were strongly positive: gold sol curve was 0000000210. The Wassermann reaction was negative in blood and spinal fluid. Following the lumbar puncture, she complained of continuous and severe pain in the nape of the neck.

Examination on January 21 revealed: on the right slight ptosis, enophthalmos and myosis, and inconstant nystagmus to the left. Both upper limbs were generally weak, but not spastic. Diaphragmatic movement on both sides was poor. The lower limbs showed no weakness.

There was no loss of tactile sensation, but a definite hypalgesia over the second to 4th cervical segments on both sides. Sense of passive movement was lost at all joints of both upper limbs, preserved but impaired in the lower imbs.

Vibration was not appreciated over the clavicles, acromion processes, elbows and wrists on both sides, but faintly appreciated over the fingers, ribs, iliac crests and lower limbs.

The tendon-jerks in all four limbs were abnormally brisk and equal on the two sides, the abdominal reflexes were absent, and both plantar responses were extensor. Sphincter control was unimpaired.

Operation.—Mr. Julian Taylor operated on January 23. On rotating the cord, he discovered an endothelioma the size of a large walnut attached to the dura upon the left antero-lateral aspect of the cord. About one-fourth of the tumour extended above the rim of the foramen magnum. The patient rallied well from the operation, and was comfortable next day, but died suddenly from respiratory failure twenty-four hours after operation.

Post-mortem examination showed the tumour to have been completely removed.

DISCUSSION.

Having described our cases in detail, we propose to discuss the symptoms of the group as a whole under the several headings already used.

In Cases 1 to 4 and in Case 7, the level of maximal compression was below the foramen magnum, though in each case a part of the tumour extended above it. In Case 5 the level of compression was at the lower border of the atlas. In Case 6 the compression was above the level of the foramen magnum, only a small portion of the aneurysm extending below it. The part of the circumference of the cord or medulla subject to direct compression was in Case 1, right lateral; Case 2, right posterolateral; Case 3, right anterolateral; Case 4, anterior; Case 5, anterior; Case 6, right posterolateral: Case 7, left anterolateral.

Involvement of cranial nerves.—As was to be expected, owing to the level of the lesion, the 11th and 12th cranial nerves were severely affected in Case 6. The impairment of sensation in the trigeminal field was of a type and distribution which suggested involvement of its descending sensory root. In addition vertigo and nystagmus were prominent. In Case 3, in which there was a considerable extension of the tumour above the foramen magnum, there were post-operative developments of interest. The involvement of the 11th cranial nerve was almost certainly due to traction upon it in the course of removal of the tumour (as also in Case 1). In this instance there was also evidence after operation of damage to the afferent trigeminal pathway, either the descending spinal tract or the nerve itself. The distribution of the sensory loss and abolition of corneal reflex suggest the latter.

Apart from Case 6, however, signs of cranial nerve involvement before operation were little in evidence. In Cases 2, 3 and 5 there were none. In Case 1 the tongue was protruded slightly to the right. In Case 4 on a single occasion a fine nystagmus was observed, as also in Case 7.

Elsberg [2], apropos of tumours between the 1st and 3rd cervical segments, states that cranial nerve symptoms are surprisingly infrequent, and signs referable to cerebellar disturbance very unusual. He mentions nystagmus, trigeminal hypæsthesia and facial weakness as occasional findings.

Abrahamson and Grossman [1], in five cases of compression at the level of the foramen magnum, observed nystagmus in two, but no other affection of the cranial nerves.

Rhein [9], in a report of a single case, records weakness of the right soft palate associated with dysphagia and dysphonia in an endothelioma filling the foramen magnum.

In Frazier and Spiller's case [5], of an endothelioma whose major bulk was above the foramen magnum and on the left side, there was atrophy of the left trapezius, and a marked fibrillary tremor with wasting of both sides of the tongue.

Globus and Strauss [7] make no mention of cranial nerve palsies in a case of endothelioma at the first cervical level with a small protrusion through the foramen magnum.

Kraus and Silverman [8] record unilateral lower facial paresis as occurring in seven out of ten cases of tumour at the high cervical level. Of these seven, five were extramedullary and two intramedullary.

Elsberg and Strauss [4] observed slight nystagmus to the left in a case of endothelioma, of which about one-third projected upwards through the foramen magnum.

It appears on the whole that, in the group of cases which form the object of this study, a tumour which does not extend above the foramen magnum is unlikely to cause any symptoms referable to the cranial nerves, and that a tumour which straddles the edge of the foramen magnum is likely to cause symptoms of spinal cord compression of a kind and degree which overshadow any cranial nerve symptoms that may be present. If such symptoms are much in evidence before operation a large part of the tumour is probably above the foramen magnum.

The cervical sympathetic.—Some evidence of cervical sympathetic palsy was present in four of our cases (1, 3, 4 and 7). It appears to have been present in two of the six cases reported by Elsberg and Strauss [4] in which a tumour projected from spinal canal into foramen magnum. Cervical sympathetic palsy, therefore, seems to be an inconstant phenomenon in the syndrome under consideration.

Motor system.—In all seven cases spastic weakness of the limbs was prominent among the symptoms. In cases 1, 2, 3, and 6, in which the compression was to one side of the mid-line, the weakness was first noticed in the ipsilateral upper limb, then in the lower limb of the same side. In cases 2 and 3 the weakness subsequently progressed to involve the contralateral lower limb. So far as our experience goes, therefore, it confirms on the whole the observation of Elsberg already quoted, that in high cervical tumours the involvement of the limbs follows an order in which the ipsilateral upper limb is involved first and the contralateral upper limb last. Case 7 was exceptional in that no signs of pyramidal disease appeared till after lumbar puncture. The weakness when it did appear was confined to the upper limbs and affected both equally though the tumour was laterally placed.

Localized muscular wasting was present in five of our cases. In Cases 5 and 7 it was absent. In Case 4 there was generalized muscular wasting of both upper limbs. This was the case in which the compression was anterior. In the other four cases the compression was anterolateral, lateral or posterolateral, and in each, at one time or another, wasting of the intrinsic muscles of the ipsilateral hand was a striking feature. In Cases 2 and 3 it developed after operation, and in Case 3 was of sufficient degree and duration to be attended for a while by a *main en griffe* deformity.

Many observers in the past have commented upon the occasional occurrence of atrophy in the hand as the result of a lesion at a higher level in the cervical cord than would be considered appropriate in the light of accepted anatomical fact. Garcin *et al.* [6] report a case in which an endothelioma at the 5th cervical level gave rise to pronounced atrophy in both hands as well as in the shoulder girdles, so that the diagnosis of amyotrophic lateral sclerosis was first suggested.

Elsberg and Strauss [4] state that "atrophy of the muscles of one or both fore-arms and of the intrinsic muscles of the hands is frequent, not only in tumours which involve the lower half of the cervical cord but in those above the 4th cervical segment." We have no explanation to offer for this phenomenon. It may be due to a descending arterial supply to the motor cells concerned, which is liable to interruption as the result of compression at the level of the foramen magnum. As a fact of clinical observation the point is clearly of great importance, for misinterpretation may easily lead to a diagnosis of syringomyelia.

Paralysis of the diaphragm from a lesion at the first cervical level is also somewhat unexpected. Yet it occurred without doubt in Case 6 in association with an earlier story of hiccough. Frazier and Spiller's case [5] provides a comparable example—an endothelioma astride the edge of the foramen magnum, and indenting the left lateral aspect of the cord at this level, with paralysis of the left half of the diaphragm in addition to other symptoms and signs.

Sensation.—Of the *subjective complaints*, pain referred to the second cervical distribution on one or both sides, especially if, as in Case 1, followed by numbness, is a symptom to be expected when the lateral or posterolateral aspect of the cord is directly compressed. The importance of this symptom as a diagnostic point has been stressed by Elsberg and Strauss [4]. When present, it frequently precedes all other symptoms by a considerable interval. Cases 1 and 7 provide striking examples.

The sensation as of a tight band or collar around the upper part of the neck was a prominent symptom in Case 7, preceding the appearance of abnormal physical signs.

In the four laterally situated tumours of our series, pain, tingling or numbness referred to the ipsilateral arm, fore-arm and hand, was an early symptom in all. Comparable symptoms were also referred to one upper limb in Cases 4 and 5 in which the compression was anterior.

In Case 1 the numbness was confined to the thumb, middle and ring fingers of the right hand; in Cases 2 and 6 pain and tingling was more vaguely referred to the whole right arm and hand. The initial symptom in Case 3 is of extreme interest in its physiological aspect, the patient experiencing momentary paræsthesiæ in the right upper limb under a particular kind of emotional stress. Somewhat akin is the hyperalgesia or over-reaction experienced in the ipsilateral limbs in Case 1. The fact of great clinical importance is that in each of our seven cases subjective pain or paræsthesia was an early symptom, that in each case this symptom first appeared in one upper limb, and that the upper limb involved was that first affected by spastic weakness.

This association of sensory with upper neuron motor symptoms in the same upper limb in the early story of high cervical tumours has been the subject of comment by previous writers (Elsberg [2], Elsberg and Strauss [4], Frazier and Spiller [5]). It is not easily explained. The sensory symptoms clearly cannot be attributed to pressure by the tumour upon appropriate roots, but must be due to interference with some intramedullary pathway. It is easier to assume that this pathway is the posterior column than to offer any alternative explanation consistent with the accepted tenets of anatomy and physiology.

The practical importance of this combination of symptoms lies in the fact that the story of progressive numbness and weakness of hemiplegic distribution may easily suggest the diagnosis of cerebral rather than spinal tumour. This diagnosis had indeed been considered in Case 1.

The next development in the sequence of subjective sensory symptoms in each of our five cases with lateral compression was that of paræsthesiæ in the contralateral upper limb. The distribution and character of these paræsthesiæ as they first appeared were thus described:—

Case 1.—This patient, a medical woman, spoke of "coldness along the ulnar border of the left hand and arm."

Case 2.—The patient was a Jewess with little English at her command, and described only tingling in the left hand.

Case 3.—"Numbness in the left little finger gradually spreading across the hand to include the other fingers and thumb."

Case 6.—"Numbness of the little and ring fingers" spreading up the inner border of the forearm to the elbow.

Case 7.—"Numbness in the right hand."

The correspondence of distribution in three of these five cases is so close that it must surely be related to the position of the lesion. In each instance the right lateral aspect of the cord was compressed at the level of the foramen magnum. The observation suggests that at this level there is some anatomical arrangement of the fibres in the spinothalamic pathway which results in those from the hand, and especially from the ulnar side of the hand, lying most superficially. Some such arrangement has been postulated by Tilney and Elsberg [12], but their diagrams would not explain our observations. They postulate a lamellation of the fibres so that those from the sacral segments lie most superficially and posteriorly. Pressure. therefore, upon the anterolateral aspect of the cord might at first spare the lower, and pressure on its posterolateral aspect, the upper segments. But in both Case 2 (posterolateral) and Case 3 (anterolateral) the early reference of parœsthesiæ to the lower rather than the upper cervical segments was associated with some degree of preservation of sensibility in the sacral segments.

The character and distribution of the *objective sensory loss* in our cases corresponds on the whole with what has been observed by others in compression of the cord at this level. Elsberg and Strauss [3, 4] in particular have emphasized the dissociated character of the cutaneous sensory defect. A severe degree of loss to painful and thermal stimuli may be associated with a normal response to tactile stimuli as judged by clinical standards. Furthermore, there may be not only dissociation between the response to heat and cold, but between thermal and other kinds of pain.

These observations are confirmed in every point by our own observations. In relation to the persistent area of over-reaction to cold in the thoracic region in Case 3, we are impelled to quote Elsberg [2 verbatim: ". . . in many cases the patient is unable to recognize hot at a time when he is still able to recognize extreme cold. . . . In some instances hot is not recognized at all, but cold, though not recognized as such, is distinctly painful. . . . It is a very interesting fact that this perversion of cold in which cold is not recognized as such, but is felt as pain, may be found over areas in which pain as tested with a sharp needle, and even pain due to deep pressure, has been entirely abolished." Practically the recognition of the occurrence of such dissociated anæsthesia in high cervical tumours is of importance in the differential diagnosis from syringomyelia.

In each of the five cases in which the tumour was laterally placed there was some sensory defect *on the same side as the lesion.* In four of these cases the defect was confined to the area of the upper cervical segments (Cases 1, 3, 6 and 7). In Case 2 it was much more extensive. The distribution of the *contralateral* cutaneous sensory defect in Case 1 covered all segmental areas up to and including the second cervical, but with an ill-defined upper level. The distribution in Case 2 was similar, but with relative sparing of the sacral segments. Again, the upper level of sensory defect was indefinite. In Case 3, in which the tumour was anterolateral, the upper level was sharply defined, and corresponded exactly with the boundary between the trigeminal and second cervical fields. In this case the relative sparing of the lower thoracic segments for pain and cold was a striking feature, and there was also sparing of the sacral segments for heat only. In Case 6 the maximal defect was confined to strips of roughly segmental distribution in the upper and lower limbs, with less involvement of the rest of the limbs and upper trunk, and escape of the lower trunk.

In Case 7 the contralateral as well as the ipsilateral defect was confined to the upper three cervical segments.

In Case 4, in which the compression was anterior, at the first examination the sensory defect was confined to the medial border of right upper limb and right trunk, and in Case 5, again with anterior compression, there was impairment over the 2nd to 4th cervical segments on both sides, and below this, over the whole of the limbs and trunk on the right.

The simplest explanation of the bilateral defect in the upper cervical segments observed in several of these cases is that, at the level of compression there was impairment of conduction, not only in the spinothalamic fibres, but in those of the root entry zone on both sides.

The relative and absolute escape from sensory loss of large segmental areas on the trunk observed in Cases 3 and 6 respectively, aroused in each instance the suspicion that there might be two separate lesions of the spinal cord at different levels. This possibility was disproved at post-mortem in Case 6, and the post-operative course in Case 3 makes it highly improbable that there was a second lesion in this case. Such escape of intermediate segments depends presumably upon a lamellar arrangement of the fibres in the spinothalamic tracts, as has been suggested by Tilney and Elsberg [12], though it cannot be explained in terms of the pattern which they represent.

Sensory defect of the type which depends upon interference with the posterior columns was a conspicuous feature in six cases, but conspicuously absent in Case 1. In this case, the position of the tumour in relation to the transverse section of the spinal cord (lateral) differed very little from that which obtained in Cases 2, 3 and 7 (posterolateral and anterolateral), but in the latter cases the disturbance of posterior column function was severe; in these three cases, however, as also in the others of this series, the degree of compression of the cord as a whole, as judged by the clinical evidence, was considerably greater than in Case 1. In Cases 4 and 5, in which the cause of compression was anterior, there was extensive and severe loss of posterior column function, but this was at a stage when bilateral spastic weakness was advanced. Our conclusion, therefore, is that in compression at this level, the time of onset of posterior column involvement depends rather upon the degree of compression of the spinal cord than upon the site of incidence of the compression in relation to the circumference of the cord. This view is in agreement with that of Elsberg [2] who states as a rule that disturbance in vibratory and articular sense in spinal tumours always occurs when the pressure has affected the entire thickness of the cord, whether the growth is ventrally or dorsally placed. Dissociation between defect in the sense of passive movement and that of vibration was evident in Cases 2 and 5, in which there was loss of vibration with preservation of postural sense, and to a lesser degree in Case 6, in which vibration sense was partly preserved, while postural sense was lost. Similar dissociation may be sometimes observed in cases of intramedullary disease, for instance, in tabes, subacute combined degeneration, and disseminated sclerosis. Its occurrence in compression of the cord by tumours has before been noted by Elsberg [2]. The distribution of the defect of posterior column sensibility in Cases 2, 3, 5 and 6 conformed to a type which we suggest may be a characteristic feature of compression of the cord at this level at certain stages in its development. In Case 2, vibration sense was lost over the whole right upper limb and clavicle, unimpaired elsewhere; postural sense was impaired in the right fingers. In Case 3, vibration sense was lost over the trunk and both upper limbs, including the clavicles and iliac crests, and in right lower limb, unimpaired in the left lower limb. Postural sense was lost in both hands, slightly impaired in the right lower limb, unimpaired in the left lower limb. In Case 5, vibration sense was lost over the right trunk and limbs up to and including the acromion process, and over the left lower limb, preserved over left trunk and upper limb. Postural sense was defective in the right thumb, elsewhere normal. In Case 6 vibration sense was impaired in the right upper limb up to and including the clavicle. Postural sense was lost in both upper limbs, unimpaired in the lower limbs. In Case 7 both postural sense and vibration sense were lost in both upper limbs (including loss of vibration sense over the clavicles), with partial loss in the fingers and relatively little defect in the lower limbs.

Thus in each of these cases the defect of posterior column sensibility, as measured by one or other test, was practically confined to one or both upper limbs. This distribution suggests that the fibres which enter the posterior columns from the posterior root entry zone at first lie superficially, and thus suffer first and more severely from the effects of compression. Evidence in favour of a strictly lamellar arrangement of the fibres in this fashion is provided by the observations made in Case 3 during the stage of recovery, when the defect of postural sense was minimal in the fingers and wrist, greater at the elbow, and maximal at the shoulder, and vibration sense remained impaired over the acromion after it had returned to normal over the remainder of the upper limb.

It is worthy of note that in Cases 2 and 3 the post-operative return of posterior column function from severe impairment to normal took only a few weeks. It is probable that the development of this form of sensory loss during the progress of compression may be equally rapid. This was shown in Case 7 and appeared to be so in Case 4, in which, however, the patient's inadequate ability to co-operate over sensory tests impaired the value of the observations.

Reflexes.—The disturbances of reflex function need little comment. Massive reflex movements of the upper limbs of the type described by Buzzard and Riddoch [10] were observed in Cases 3 and 5 only.

Sphincter control.—In Case 5 only was there any disturbance of sphincter control. This is in opposition to the opinion expressed by Abrahamson and Grossman [1] that bladder and rectal disturbance occur early and are frequently the first symptoms in cases of high cervical tumour. Stookey [11], however, as the result of an analysis of a series of cases of spinal tumour with reference to this point, concluded that above the level of the conus there was no relation between the level of the lesion and the time of onset of sphincter disturbance.

Vertebral column.—Clinical examination revealed some abnormality of the cervical spine in each case, though in no instance was this striking. It was observed only when especially looked for. In the five cases of tumour, active or passive movement of the head upon the neck in one direction or another was associated with, and limited by pain. Tenderness on pressure over the upper cervical spines was present in Cases 1, 2, 4 and 5, but only severe in Case 4.

Cerebrospinal fluid.—In Cases 5 and 6, Queckenstedt's test was negative and the protein content in the fluid was within normal limits. It is to be noted that these were the two cases in the series in which the compression was not due to new growth.

The five cases of tumour all showed some abnormality. In Case 1 Queckenstedt's test was negative. In the other four cases, on jugular compression, either the rise, or the rise and fall of pressure were slower than the normal. In Case 1 the protein was slightly raised (80 mg. on the first and 60 mg. on the second occasion). In Cases 2, 3 and 4 it ranged from 100 mg. to 200 mg., whilst in Case 7 it was 1,200 mg.

These findings correspond with what may be observed in extramedullary tumours at other levels, except that the degree of subarachnoid block in relation to the severity of the clinical symptoms, would appear to be less in these cases of high cervical tumour than it is at lower levels. Of particular interest was the exceptionally high protein content in Case 7 with evidence only of partial block at a stage when no abnormal physical signs had not yet been discovered.

X-ray examination.—No abnormality of the cervical spine was seen in any case. A cisternal puncture for the purpose of lipiodol injection was attempted and failed in Cases 1 and 2. It is probably a dangerous procedure in compression at this level, and unlikely to give successful results. Injection of lipiodol by lumbar puncture, and examination on the tilting table, head downwards, appeared to be the method most likely to provide visual evidence of the lesion. It was used in four cases with variable, and, on the whole, disappointing results.

In Case 1 only was the lower border of the tumour accurately defined. In Case 3 there was no adequate movement of the lipiodol, although the patient was tilted head downwards for several minutes. In this case, the degree of subarachnoid block was considerable, and the residual pressure after withdrawal of cerebrospinal fluid was 5 mm. It seems possible that the lipiodol injected forty hours later found the subarachnoid space empty and collapsed, and was unable with the aid of gravity to force a passage. After the event, we considered that we should have injected enough saline to fill the subarachnoid space before introducing the lipiodol.

In Cases 2 and 5 the results of this examination were misleading. The flow of lipiodol was arrested at the level of the 6th and 5th cervical vertebræ respectively. In each instance the movement of the lipiodol as viewed with the screen was steadily maintained up to the level of arrest.

All the observations were made through the generosity and with the help of Dr. H. M. Worth, and the same technique used in each case. We have no explanation to offer for the discrepancies, but conclude that in the reversed position of the body, arrest in the upper cervical region, unless it shows the convex outline of a tumour, is not to be relied upon as a guide to localization.

The early symptoms in cases of tumour.—The five cases of tumour (four endotheliomas and one neurofibroma) form a group of more or less uniform pathology, all being fibrous growths of slow development. In all save one pain at the back of the head and neck was the earliest symptom. The exception was Case 4, in which the tumour lay on the anterior surface of the cord; here paræsthesiæ and weakness in one upper limb were the earliest symptoms, and a vice-like pain at the back of the head appeared only as a late symptom.

In the other cases, suboccipital pain was the leading or only complaint for months or years before other symptoms developed. In Cases 1 and 7 it continued as the only symptom for five and three years respectively. In Case 2 it preceded other symptoms for about one year. In Case 3 it was the leading symptom for about one year, being associated with occasional paræthesiæ in one arm.

After the suboccipital pain, paræthesiæ in one or other hand was the next symptom to appear in all five cases. In Case 7 these symptoms were followed by the band-like sensation around the neck. In this case the rapid development of physical signs following lumbar puncture was of particular interest. After a period of nearly four years, during which the symptoms were entirely subjective, the signs of compression were fully developed within three days of the removal of 4 c.c. of cerebrospinal fluid.

NOTE ON THE SURGICAL APPROACH (JULIAN TAYLOR).

To expose the foramen magnum it is best to have the patient lying belly downwards with the neck flexed. Flexion of the neck may embarrass respiration where there is foraminal block, and thus the degree of permissible flexion must be determined in consultation with the anæsthetist before the operation is begun, but the technical advantage afforded is so great that the flexed position cannot altogether be abandoned on account of possible danger. The scalp and neck are incised in the middle line from the external occipital protuberance downwards and the first three cervical arches are removed. The dura is inspected and the presence or absence of respiratory pulsation is noted. If it be clearly seen in the suboccipital region it is certain that a tumour, if present, is well below the foramen, especially where cerebrospinal fluid block has been previously demonstrated. Respiratory pulsation of the normal theca in this region is of such amplitude that its observation leaves little opportunity for error, either in recognition or in consequent deductions regarding the level of a possible tumour. If a tumour blocking the foramen be thought to be present, part of the occipital bone is then removed, a fairly extensive craniectomy being advisable. The dura of the posterior fossa and the spinal theca are then opened above and below the foraminal constriction and the incisions are joined. The advantage accruing from the large craniectomy is then seen if, as the result of tumour growth in the foramen, the normal venous sinuses of the dura be found greatly increased in capacity and number. On opening the dura and exposure of the arachnoid the earlier observation regarding pulsation is checked. With inspiration and expiration the ebb and flow of fluid through the unobstructed foramen is so freely tidal that there is now no possibility of erroneous deduction, but if pulsation be absent something is unquestionably blocking the foramen, and thus if no tumour be seen there must nevertheless be one situated either in the central nervous substance or anteriorly. A cerebellar tumour is at once obvious, but at this stage, unless there is evident lateral displacement of the medulla, it may be difficult to distinguish between a medullary tumour and one anteriorly placed. An anteriorly or anterolaterally placed growth almost necessarily entails division of the first and perhaps the second posterior cervical roots, a step that usually permits the operator to rotate the medulla far enough to gain a view of what lies in front. It will usually afford enough room to enable him to remove a tumour, but the anterior roots and the accessory nerve may sometimes be in the way. The decision to divide even posterior roots may be a difficult one to make in the case of a patient whose diaphragm and intercostal muscles are paralysed and whose breathing is precariously dependent on the intact accessory and second cervical nerves.

When a neurofibroma has been found it is obviously necessary to remove a part of the affected nerve root, and when an endothelioma is present there are usually adhesions to the surrounding nerves, dissection of the tumour from which must be carried out with the precision that the situation demands. The removal of an endothelioma may at first appear to present formidable difficulties, but a successful attempt to free the tumour from its dural attachment may render it unexpectedly docile, when removal may be effected without difficulty. It is obvious that the force of manipulations in this region is transmitted undiminished to the medulla, and thus that sudden fluctuations in the pulse frequency, blood-pressure and respiration may be experienced. If the operator therefore finds this part of his task anything but effortless, or if his attempted division of a dural attachment has failed, he must then proceed to remove pieces from the accessible part of the tumour, in order that the remaining deeper part may be more easily displaced. For this purpose the writer's preference is the use of the knife to that of the diathermic cautery owing to the proximity of the vital medullary centres. These endotheliomas have not been highly vascularized and there has been little bleeding on incising the tumours. The bared dura may, however, bleed freely from opened veins, but the hæmorrhage is easily stopped by a temporary application of muscle grafts. The occipital bone is sometimes invaded by the growth, in which case the operator must decide for himself whether in a life-saving operation of this sort he should undertake the technically difficult, but pathologically correct, procedure of removing affected bone from the anterior or lateral part of the foraminal edge. The bone here normally encloses venous lakes and these may well be increased by endotheliomatous invasion. The tumour gone, there appears at once the respiratory ebb and flow of fluid from the posterior fossa, and even if the respiration and pulse have been seriously affected by the manipulations there soon returns a good pulse and regular breathing of satisfactory depth. The wound is then closed in the ordinary way by suture of the muscles and skin. As in other procedures in the posterior fossa the operator must be prepared for reactionary depression of the respiratory and cardiovascular functions during the hours following the operation.

REFERENCES.

[1] Abrahamson, I., and Grossman, M. *Trans. Amer. Neurol. Association*, 1921, 149.
[2] Elsberg, C. A. "Tumors of the Spinal Cord," 1925.
[3] *Idem. Arch. Neurol. and Psychiat.*, 1929, **22**, 949.
[4] Elsberg, C. A., and Strauss, I. *Ibid.*, 1929, **21**, 261.
[5] Frazier, C H., and Spiller, W. G. *Ibid.*, 1922, **8**, 455.
[6] Garcin, R., *et al. Rev. Neurol* , 1933, 40, **1**, 391.
[7] Globus, J. H., and Strauss, I. *Arch. Neurol. and Psychiat* , 1929, **21**, 1330.
[8] Kraus, W. M., and Silverman, N. E. *Journ. Neurol. and Psychopath.*, 1926, **7**, 132.
[9] Rhein, J. H. W. *Arch. Neurol. and Psychiat.*, 1924, **11**, 432.
[10] Riddoch, G., and Buzzard, E. F. *Brain*, 1921, **44**, 397.
[11] Stookey, B. *Arch. Neurol. and Psychiat.*, 1923, **10**, 519.
[12] Tilney, F., and Elsberg, C. A. *Ibid.*, 1926, **15**, 444.

MULTIPLE MENINGEAL AND PERINEURAL TUMOURS WITH ANALOGOUS CHANGES IN THE GLIA AND EPENDYMA (NEUROFIBROBLASTOMATOSIS).

WITH REPORT OF TWO CASES.

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INTRODUCTION.

IN the *Edinburgh Medical and Surgical Journal* for 1822 there appeared an article by J. H. Wishart, entitled "A Case of Tumours in the Skull, Dura Mater and Brain." His patient was a youth, aged 21, who complained of bilateral deafness of recent onset and of a small tumour on the back of his head. Two years later he was absolutely deaf and blind, the pupil of the left eye being "completely dilated as in a case of amaurosis." The patient had been blind in the right eye since soon after birth. The tumour on the back of his head had grown considerably and it now caused him a great deal of pain. He experienced "very peculiar and disagreeable smells," severe frontal headaches and attacks of vomiting, and died soon afterwards. The autopsy was performed by Wishart, who found numerous tumours attached to the dura mater, most of them arising from the falciform process. A tumour about the size of a split pea and of considerable hardness was attached to the left 5th cranial nerve, while on that of the right side were several small nodules. There was a tumour attached to each "7th nerve" (in all probability the 8th nerve is meant) just at the entrance to the internal auditory meatus. Multiple tumours were found upon the nerve-roots throughout the whole extent of the "medulla spinalis." Wishart concluded that "it is most probable that these tumours on the nerves arose rather from the dura which envelopes them than from the nervous substance itself."

Similar cases have been recorded from time to time, but Wishart's appears to be the first to be published. In a review of the literature of multiple meningeal tumours, Hosoi (1930) collected ten examples of this particular type, including one of his own. Three other cases occur in the literature prior to 1930, those of Soyka (1877—first case), Kaulbach (1906) quoted by Stewart and Copeland, and of Christin and Naville (1920). Since the publication of Hosoi's paper, further examples have been recorded by Kernohan and Parker (1932), Katzenstein (1932), Cabot and Smith (1933) and by Shapland and Greenfield (1935).

This syndrome of multiple meningeal tumours associated with neurofibromata (of which there are apparently seventeen cases on record) is but one variety of the not uncommon disease of the central nervous system "central neurofibromatosis," or "central von Recklinghausen's disease." The former term has been in common use since 1900, but apparently it was not employed by von Recklinghausen himself.

Papers by numerous authors have dealt with the ætiological, clinical and pathological aspects of "neurofibromatosis," but there is still some lack of agreement as to the correlation and exact nature of the pathological lesions. It is the purpose of the present communication to record details of two further examples of the relatively rare syndrome originally described by Wishart and to suggest a clinical and pathological classification of "neurofibromatosis."

Case 1.—C. K., male, a house painter, aged 25, was admitted to the West End Hospital for Diseases of the Nervous System, London, on September 12, 1932, complaining of "dizziness, headache and noises in the ears." The total duration of illness prior to admission was eight years.

Eight years previously (1924) appendicectomy was performed in another hospital, the appendix being retrocæcal and containing pus. According to the notes he looked pale and ill and had conjunctivitis (whether unilateral or bilateral not stated). A month or two later he noticed the right eye bulging and a discharge from the right nostril. He returned to hospital with proptosis of the right eye, the movements of the eyeball being of full range. "Nasal polypi" were found on several occasions and removed. A note at this time states that congenital cataract was present in both lenses.

Two years later (1926) he was readmitted to hospital on account of a return of the right-sided nasal obstruction and discharge. Operation was performed for what was described as a right ethmoid "mucocœle" and a right-sided "nasal polypus." The right frontal sinus was intubated. The right eye was proptosed, but both pupils reacted to light and on accommodation. After the intubation there was no noticeable change in the condition of the right eye.

A year later (1927) he was unable to extend fully the middle finger of his left hand. Within a fortnight the weakness had spread to involve the extensors of all the fingers of the left hand. After a month or two wasting and gradually increasing weakness of the whole of the left leg developed.

Three years later (1930) he was again admitted to hospital in a condition very similar to his present state (1932) with the exception that he had, at that time, no defect of speech. A biopsy was performed on a small tender nodule found on the back, the report stating that it was a "typical neurofibroma."

Six months later (1931) he began to lose sight in the right eye, and a few months later became deaf on the left side. Early in 1932 he complained of headache for the first time, frontal in situation, severe and continuous, and aggravated by movement.

In June, 1932, he was admitted to the Metropolitan Hospital under the care of one of us (C. W.-D.). Here a biopsy was performed on a small portion of tumour removed from right orbit. The report stated that it was an "endothelioma showing psammoma-like bodies."

The patient was later transferred to the West End Hospital for Diseases of the Nervous System.

Past history.—He had never been robust. Between 1925 and 1928 (i.e. seven years before admission to this hospital) he had had four attacks of pleurisy, but paracentesis thoracis had never been performed. There was no history of fits. He was moderate in the use of alcohol and tobacco.

Family history.—He was one of a family of eleven, of whom seven and also both parents were still alive and well. There was no family history of mental disease, epilepsy, deafness, paralysis, skin-tumour or moles.

Condition on examination (*September*, 1932).—The patient was a poorly nourished pale young man of slender build with no clinical indication of endocrine dysfunction. There was a marked degree of proptosis of the right eye, which was totally blind. Its movements were restricted in all directions. The pupil was circular, central, regular, and of normal size, but its reactions to light and on accommodation were sluggish. The fundus could not be seen on account of an intraocular opacity.

The visual acuity of the left eye was poor, but he could recognize fingers at one foot. The pupil was central, regular and of normal size; its reactions to light and on accommodation were sluggish. The ocular movements were of full range, with fine nystagmus in all directions. The fundus showed some four dioptres of papillœdema, but accurate measurement was difficult owing to a semicataractous lens. No retinal tumours were identified. During sleep the left eye remained partially open.

The left corneal reflex was diminished, but the motor functions of the 5th cranial nerves were intact. A left-sided facial paralysis of the infranuclear type with slight muscular wasting was present. There was complete nerve deafness on the left side and partial on the right. The right side of the tongue was weak but not wasted. Speech was loud and somewhat explosive. The functions of the other cranial nerves were not impaired.

Upper extremities: There was left-sided wrist drop with wasting of the extensor group of muscles of the forearm. The supinator jerk was absent on this side but present on the right. The biceps and triceps jerks were present on both sides, but brisker on the right.

Lower extremities: The calves and thighs on both sides were wasted, more so on the left. Fibrillary tremors were observed in the wasting muscles. Bilateral pes cavus was present. The right knee-jerk was exaggerated, the left absent. Both ankle-jerks were absent. The right plantar response was flexor, the left extensor. The abdominal reflexes were present on the right, but absent on the left side.

Sensation: Owing to the patient's deafness observations were difficult. There appeared, however, to be a diminution in sensation to pinprick over the areas supplied by both 5th cranial nerves, and diminution of pain sensation over the left forearm on distribution of the 8th cervical root. Vibration and deep pain were appreciated in both lower extremities. The contour of the spine was normal and all its movements full.

The patient's gait was very ataxic, but there were no tremors at rest. The bladder was not distended; micturition and condition of the urine were normal.

No swellings were palpable on any of the peripheral nerves and there were no cutaneous manifestations of neurofibromatosis, apart from the nodule removed from the back for biopsy at an earlier stage, or of tuberous sclerosis, i.e. he had neither *café au lait* patches, vitiligo nor nævi, either vascular or pigmented, nor adenoma sebaceum. There were no palpable irregularities in the contour of the skull or of the long bones.

The chest was poorly covered and expansion diminished. No abnormality was detected in the heart or lungs; the average pulse-rate was 100. The blood-pressure varied between 105/70 and 90/60. No abnormality was detected in the abdomen. The liver, spleen and kidneys were not palpable.

He appeared of average intelligence and his behaviour in the ward was in every way normal. He co-operated as well as his deafness would allow and was quiet and composed, exhibiting no evidence of euphoria.

Investigations.—The cerebrospinal fluid, eight weeks before death (Dr. H. C. Lucey) was yellowish and under considerable pressure. No clot formed on standing. Four small lymphocytes were present per c.mm. Total protein was 0·1 per cent. The Wassermann reaction was negative in both the fluid and blood.

Electrical reactions (Dr. Sainsbury): Faradic responses were easily obtained in all muscles of the left arm except in the extensor communis digitorum and extensor longus pollicis. In these latter muscles complete reaction of degeneration (R.D.) was present and no galvanic reactions were obtained. In the lower extremity all responses were easily elicited except in the tibialis anticus and the intrinsic muscles which showed absolute R.D. Faradic responses were obtained on the left side of the face and the galvanic reactions were fairly brisk.

Progress of case.—Repetition of lumbar puncture was not considered justifiable as the patient's condition had rapidly become worse. Headache was considerable, partial relief being obtained with intravenous hypertonic saline. He died on October 29, 1932, after twenty-four hours' coma. Throughout his stay in the Metropolitan and West End Hospitals he remained apyrexial and had no fits.

AUTOPSY.

The body was that of a fairly tall emaciated young adult male, with no appreciable difference in the size of the two lower limbs, but with more marked atrophy of the extensors of the left than of the right forearm. No nævi or patches of pigmentation in the skin and no subcutaneous nodules were found. There still remained a moderate degree of proptosis of the right eye, the pupil of which was distinctly larger than that of the left.

Cranium: No subcutaneous nodules were found in the scalp. The skull-cap was of moderate thickness, somewhat irregular and distinctly asymmetrical, with only scanty diploë, and with no periosteal swellings or any of the hyperostoses sometimes found in the bone over subjacent meningiomata.

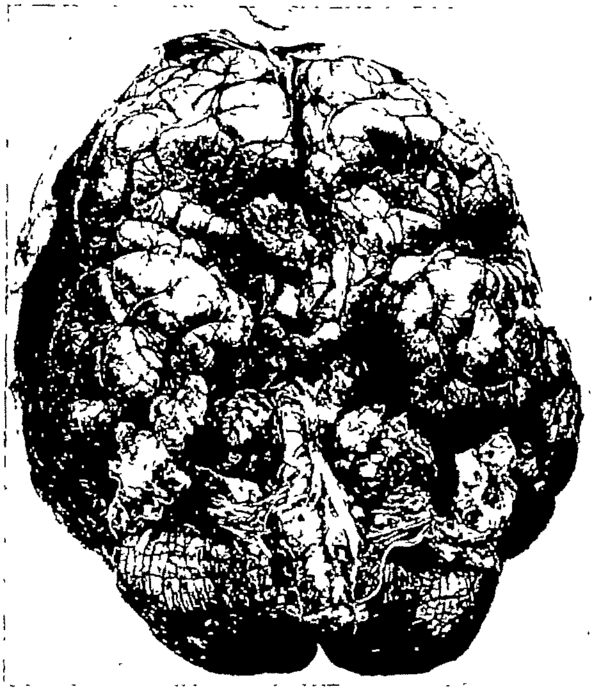

FIG. 1.—*Case* I. Inferior aspect of brain to show the meningiomatous tumour involving the right olfactory bulb. The underlying dura was infiltrated by it. On either side of the much compressed pons lie the cerebello-pontine angle tumours and, external to each of these, is a portion of the temporal bone containing the internal auditory meatus.

The dura mater was easily separated from the interior of the skull, and, scattered over its arachnoid surface, were some fifty small projecting tumours varying up to half a pea or a small bean in size, most of them firm and slightly nodulated, others somewhat friable and "cauliflower-like." The three largest, approximately equal in size and some 8 by 10 mm., projected into and indented, but were not adherent to, the surface of the hemispheres. These tumours did not show any outward infiltration nor had they caused any erosion or indentation of the bones of the skull. There were four small plaques of similar growth projecting slightly from the surface of the falx cerebri and several on the under surface of the tentorium cerebelli. A number of smaller tumour-like masses of like nature projected into the lumen of the superior sagittal sinus. Both middle ear cavities appeared healthy and were not invaded by tumour.

The brain weighed 1,450 grm. Its surface was slightly flattened and congested with a certain amount of external hydrocephalus and a small pressure-cone at the base. The olfactory bulbs were embedded in a friable gritty mass growing from and invading the meninges over the cribriform plate, through which it had passed into the upper part of the nasal cavity (fig. 1). It also extended into the right orbit and surrounded the optic nerve as far as the back of the eyeball, which itself was not invaded. At each cerebello-pontine angle there was a large irregular nodular tumour, firm in consistency and attached to the 8th nerve. That on the right side measured 24 by 23 by 22 mm., and on the left 40 by 36 by 33 mm. The left tumour had invaded the temporal bone. The lower half of the pons on each side and the anterior aspects of each cerebellar hemisphere were deeply compressed and indented. On each 3rd nerve was a tumour, that on the right measuring 3 mm. and on the left 5 mm. in diameter. On the left 5th nerve there were several small tumours up to 4 mm. in diameter: another 1½ mm. on the right 6th nerve; while the left 6th nerve did not show any visible swellings but was compressed by the acoustic nerve tumour, as was also the right 6th nerve. A string of small tumours up to the size of hempseeds was situated on the left 9th, 10th and 11th cranial nerves; and there was a similar but smaller series on the corresponding nerves of the right side.

On horizontal section through the cerebral hemispheres, several small patches with an unusual fine fenestrated appearance were found, mostly in the subcortical white matter, particularly in the right inferior frontal gyrus and in both superior parietal lobules. Other whitish and slightly depressed patches in the gray matter involved the surface and had a slightly firmer consistence than the neighbouring cortex. Over these the leptomeninges were appreciably thickened and adherent. The ventricles were slightly dilated, but without any ependymal "granulations" or nodules, and to the naked eye the choroid plexuses appeared normal. Apart from compression by the acoustic nerve tumours, there was no obvious abnormality of the cerebellum. The pituitary was of normal size.

Spinal Cord and Nerve-Roots: Numerous small irregular tumours, several hundred in number and varying in size from minute swellings just visible to the naked eye to slightly larger than a hemp-seed, were found upon the nerve-roots, particularly upon those of the cauda equina; sometimes a dozen or more were present upon a single root, and reminiscent of Alexis Thompson's description: "grains of boiled tapioca on a string." In addition to these, there was a larger nodulated mass, not unlike a miniature corncob in appearance, 33 mm. in length by 11 mm. in diameter, lying upon a nerve-root within the membranes posteriorly and somewhat towards the right at the level of the termination of the cord. This mass was loose and practically unattached save for a thin elastic thread suggestive of a blood-vessel rather than a nerve but at its lower end a definite nerve-root emerged. No tumours were visible on the filum terminale. In the upper cervical region, at the level of the lower margin of the atlas, there was an irregular, rather tufted or slightly cauliflower-like mass of growth, adherent to the inner surface of the dura, which, on microscopical examination, was a meningioma.

Most of the tumours were situated on posterior nerve-roots. The cord itself was here and there considerably distorted from compression by these tumours, and also by other tumours arising from the meninges. A certain amount of irregular cavity-formation was also present, particularly in the cervical region. Several of the spinal nerves were traced through the intervertebral foramina, but no naked-eye tumours were found upon them nor upon the intercostal nerves. No nodular masses were found upon the cervical, brachial, lumbar or sacral plexuses, nor upon the sciatic nerves and their branches, even when traced as far as the muscles of the calf.

Other Organs: Except for some fatty infiltration of the heart, nothing noteworthy was found in the viscera. No naked eye evidence of tumour formation was present in the suprarenals, in the sympathetic trunks or in any of the sympathetic plexuses. The thymus was persistent and moderately large, weighing 18 grm. The thyroid appeared normal.

HISTOLOGY.

Meningeal tumours (intracranial).—Sections through the nodules projecting from the inner surface of the dura over the cerebral hemispheres showed a moderately cellular growth with the cells and their processes arranged in definite whorl formation, but also with some palisading. In the centre of many of the whorls a small vessel in some stage of hyaline degeneration could be identified. In the more gritty and friable tumours, calcification and the formation of "brain-sand" particles had also occurred. The friable spongy mass of tumour infiltrating the meninges and bone of the olfactory grooves and neighbouring structures was of this nature, and component psammomatous bodies in grape-like clusters could be demonstrated in teased toluidin blue preparations, the stalks being represented by branching blood-vessels. Sections of several of the smaller dural nodules resembled those of the cerebello-pontine angle tumours and, except for the presence of varying numbers of concentric psammoma-bodies, many of them were indistinguishable from these. Small psammomatous tumours, larger and more cellular than the adjacent Pacchionian bodies, projected through the walls of the superior sagittal sinus into its lumen.

Cerebello-pontine-angle tumours.—Sections of these showed on the whole a "whorled" rather than a "palisaded" arrangement of the fibres, giving an appearance intermediate between the typical neurofibroma ("perineurial fibroblastoma" of Penfield), and the typical meningioma ("meningeal fibroblastoma " of Penfield). In some areas, however, "palisading" was definitely present. Parts of the tumours showed considerable reticulation with almost complete disappearance of the cells. As is often found in acoustic nerve tumours when stained by van Gieson's method, the component fibres showed a "terra-cotta" tint, rather than the usual pink colouration typical of collaginous fibres. In the more "palisaded" areas, and in those parts where the growth was evidently more active, the nuclei were plump and oval in shape, vesicular, and with a distinct nuclear membrane, the chromatin being scattered in small particles throughout. In those parts of the tumours where the fibres were thin and fully formed, the nuclei were narrower, more elongated and stained more deeply and diffusely. These tumours were comparatively non-vascular with only a few thin-walled capillaries, many of them resembling blood-sinuses. With silver impregnation and with Mallory's connective tissue-stain, the reticulin was found to be confined to the adventitia and immediate neighbourhood of the vessels. In Bielschowsky da Fano preparations no nerve-fibrils were detected.

Cerebral cortex: "meningio-angiomatosis."—For the investigation of this process sections selected from one of the patches in the posterior part of the right middle frontal convolution were stained by the Weigert-Pal method; these showed what might be described as a meningio-angiomatous condition of the cortex and a curious fenestrated appearance of the subjacent white matter, due to its spread into the latter (figs. 2 and 3). The blood-vessels of the lepto-meninges had very much thickened walls, and were in striking contrast to the sinus-like thin-walled blood-spaces seen in the acoustic and meningeal tumours. These pial vessels showed active proliferation and penetrated into the gray matter along with surface meningiomatous cells (*not* connected with the meningiomata described above). The process was thus a mixed lepto-meningiomatous and angiomatous condition of some chronicity (fig. 3). In this connection it is of interest to recall the syndrome described by Kalischer (1901), Parkes Weber (1929), and more recently by Bergstrand (1935), who regards it as comparable with central neurofibromatosis and Lindau's disease as well as with tuberous sclerosis. Lindau (1930) himself refers to certain gliomatous brain tumours characterized by abundant vascular proliferation, for which he suggests the descriptive term "nævi glio-vasculosi." The glial cells of the invaded areas also took part in the proliferative process, some of them being multinucleated and reminiscent of the "Gemästetezellen" found in tuberous sclerosis (fig. 4). The glial meshwork is much increased and the fibrils are coarse and thick. There also appears to be some patchy proliferation of oligodendroglia, and, throughout many of these areas of meningio-angiomatosis and gliomatosis, comparatively numerous surviving cortical nerve-cells are to be seen surrounded by these proliferative changes.

Choroid plexus.—Sections of the plexuses of the lateral ventricles showed in some parts considerable degenerative thickening of the cores of the villi but survival of the surface choroid epithelial cells; in other portions there was hyaline swelling of the connective tissue around the central capillaries and degeneration and disappearance of the surface cells. In Perdrau-stained preparations, concentric "brain-sand particles" were well seen, and were of much larger size than, but otherwise indistinguishable from, those of the meningeal tumours.

Ependyma.—The surface ependymal cells were absent over considerable areas but, where present, they were comparatively normal in appearance, although in places they were flattened and degenerated, with occasional small patches of subependymal gliosis containing little groups of ectopic ependymal cells, suggestive of the similar phenomenon often found in the neighbourhood of the central canal of the spinal cord. Small amyloid bodies were also distributed irregularly in considerable numbers throughout the subependymal tissues.

Spinal cord: root neurofibromata.—Sections through some of the lumbar posterior nerve-roots showed all stages in the development of the tumours from single small concentric whorls growing in and from any part of the sheath of the roots, up to the large naked eye tumours already noted. Sections stained by Perdrau's method demonstrated clearly the concentric fibrils of reticulin. The general appearance was suggestive more of a non-psammomatous meningioma than of a neurofibroma, but some of the tumours showed appearances intermediate between these two types of neoplasm. A noticeable feature was that, as these tumours gradually enlarged, the surviving nerve-fibrils tended to become expanded into a thin irregular capsule around them. It is interesting that this feature was noted in a solitary nerve tumour by Cheseldon in 1740. Transverse sections through, for example, a lumbar root showed the initial stages in the formation of the tumours (fig. 5), even the smallest having a distinctly concentric whorled structure and appearing to arise from the connective tissue sheath of the nerve-bundle. These tumours when stained by Perdrau's method were seen to have a very varying content of reticulin fibrils; in some there was a considerable amount, in others practically none.

Spinal cord: intramedullary neurofibromata.—These tumours were very similar to the above, being intermediate in type between typical meningiomata and typical neurofibromata. In the same microscopical section, and even in the same field, were seen tumours, in some parts whorled as in a meningioma and in others palisaded as in a neurofibroma.

Spinal cord: intramedullary astrocytomata.—The cervical enlargement contained an intramedullary tumour consisting of finely fibrillated spindle-shaped glial cells—a "fibrillary astrocytoma" which appeared to have developed from the grey matter; it was not an ependymoma derived from central ependymal cells, proliferating groups of which were also present in its neighbourhood.

Spinal cord: ependymal reactions and syringomyelic cavitations.—Transverse sections of the spinal cord at various levels showed a process resembling syringomyelia, most advanced in the lumbar region (fig. 6) with a considerable area of gliosis surrounding the central cavity. In the cervical and dorsal segments there was as yet no cavity-formation, but small tumour-like proliferations of ectopic ependymal cells were numerous. There was marked distortion of the cord, and degenerative changes had occurred in much of the white matter. In places a commencing proliferation of the central ependymal cells and a pericentral gliosis were visible.

Sympathetic ganglia.—Sections through a ganglion in the neighbourhood of the left suprarenal gland showed several small scattered areas of proliferation of the stroma indistinguishable from the neurofibromatous process found elsewhere in this case.

Sciatic nerve.—A transverse section through the trunk of the left sciatic nerve revealed the formation of a few minute concentrically arranged nodules similar to those found in many of the spinal nerve-roots (fig. 7). In structure they are rather reminiscent of a Pacinian touch corpuscle.[1]

The pituitary body was congested and showed some predominance of the eosinophil cells, with distinct intermingling of the pars anterior with the pars posterior, the glandular cells of the former "overflowing" into the anterior part of the latter.

The suprarenal bodies were moderately congested. Some of the dilated venous channels contained fibrin clots, in the interstices of which were many Gram-positive rods, presumably an agonal bacterial invasion. The medulla was perhaps rather unduly "reticulated," but no neurofibromatous or other obvious lesion was detected.

As pathological changes in keeping with the general features of the disease were found in the neighbouring sympathetic ganglia, some analogous process might have been expected to occur in the suprarenal medulla, but of this we found no evidence. Our opinion as to this was kindly confirmed by Dr. H. W. C. Vines, to whom we submitted sections.

The pancreas and spleen showed nothing of interest apart from chronic venous congestion. In the liver, in addition to chronic venous congestion, there was some irregular patchy thickening of the capsule, and fibrosis passing in from its deeper surface in a few places surrounded and isolated small groups of liver cells, but there was no generalized cirrhotic process. A small lymph-node from the neighbourhood of the left suprarenal body contained dilated and proliferated cavernous spaces in its medulla, apparently both lymphatic and blood-vascular in nature, and perhaps analogous to the patches of vascular proliferation found in the central nervous system. In the retinæ there were no angiomatous or other tumours.

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[1] In this connection the presence of fully formed and functioning Pacinian touch corpuscles in the actual substance of peripheral nerves is, as far as the authors' experience goes, a rare phenomenon, though common in many other situations such as in the walls of blood-vessels. In serial sections of the digital nerves and vessels of the right index finger of a female patient, aged 56, amputated by our colleague, Mr. Paterson Ross, for gangrene due to obliterative endarteritis, one of us (W. E. C. D.) found a well-formed Pacinian corpuscle situated in the interior of one of the lateral subcutaneous digital nerves at the level of the head of the first phalanx.

Case II.—F. C., male, aged 17, was first seen in November, 1933, complaining of occasional vomiting not associated with dyspepsia and unrelated to meals, and of rapid fatigue on attempting to walk.

Clinical history.—The illness had started three months previously. At first vomiting occurred almost daily, but became less frequent. His appetite remained good and he had not complained of headache or epigastric pain. He was stated to be able to walk normally for about 20 or 30 yards, after which he felt giddy and had occasionally fallen. For the past few weeks he had also experienced occasional diplopia after reading. No history of deafness or tinnitus was obtained. There was nothing of importance in his past history apart from pneumonia as a young child.

Family history.—His father died at the age of 50, of unknown cause. His mother was alive and well. Eight other children in the family were alive, healthy, and of normal stature. There was no history suggestive of neurofibromatosis or any similar disease in the family.

Condition on admission (November, 1933).—A somewhat undersized and poorly-nourished youth, looking about 12 years of age rather than his actual age of 17. There was some degree of infantilism and absence of pubic and axillary hair.

The pupils were equal, central, circular, and reacted normally and the fundi were normal. There was convergent strabismus owing to weakness of the right external rectus. Nystagmus appeared on lateral deviation to the left and right and also on looking upwards. There was partial nerve deafness on the right side. The functions of the other cranial nerves were normal, but speech was somewhat slurred.

All the intrinsic muscles of the right hand and the muscles of the right forearm were wasted and weak. There was slight inco-ordination of his right arm and tremor of the fingers. The right arm-jerks were brisker than the left. All movements of the lower extremities were possible, but there was slight general wasting of the muscles and bilateral pes cavus. The knee-jerks were brisk, the right slightly greater than the left. The ankle-jerks were moderate. Bilateral extensor plantar reflexes were obtained. The abdominal reflexes were present but sluggish. Sensation was apparently normal. He walked on a wide base and his gait was ataxic. The sphincters were unaffected.

Many scattered subcutaneous nodules and small fibroid masses were present over different parts of the body, e.g. back, calves, and in front of the right shin. They varied in size from that of a pea to that of an acorn. All were sessile and were firm to touch. They were not painful or tender. No *café au lait* patches were present. The heart and lungs were normal. The liver and spleen were not palpable. No enlarged lymph-nodes were felt. The pulse-rate averaged 80. The blood-pressure was 108/80.

Investigations.—The cerebrospinal fluid (November, 1933) contained two small lymphocytes per cubic millimetre; total protein was 0·28 per cent.; globulin was in moderate excess; the Wassermann reaction was negative; Lange, 3455432110. The blood Wassermann reaction was also negative. A blood-count showed no abnormality.

A biopsy of a subcutaneous nodule removed from the upper part of the back showed the structure of a fibroma with some degeneration of the fibres (H. C. Lucey).

Progress of the case.—The patient was transferred to the West End Hospital for Diseases of the Nervous System three months later (March, 1934). In addition to the previous symptoms, frontal headaches had appeared, there was increasing deafness in both ears and he was unable to walk without support.

Lumbar picture on April 6 (1934) showed a cerebrospinal fluid pressure of 220 mm., and Queckenstedt's test was positive. The fluid was slightly yellowish in colour and contained three small lymphocytes per c.mm.; total protein was 0·2 per cent.; globulin was in moderate excess and the Wassermann reaction was negative. The Lange curve was 3455432110.

On May 5 a large nodule was removed from the anterior tibial region of the right leg for biopsy. Microscopical examination showed a neurofibroma or fibroblastomatous tumour.

By the end of September further nodules, varying in size up to that of a broad bean, had appeared on the dorsum of the left forearm and also on the back, chiefly in the left scapular region and over the sacrum. By the end of the year (1934), papillœdema was present in both fundi to the extent of two dioptres. There was palsy of both 6th nerves and gross nystagmus. Bilateral ptosis was also present. The right side of the face was weak and the tongue deviated to the right on protrusion. The bilateral nerve deafness was more pronounced. Speech was practically unintelligible. There was a flaccid paralysis and muscular atrophy of the right arm and its deep reflexes were absent. Both arms were inco-ordinate. Both legs were considerably wasted, but the knee and ankle-jerks were exaggerated, the right being brisker than the left. Both plantar reflexes were extensor and the abdominal reflexes were absent. He was unable to walk, and his general condition was very poor.

During the next three months his condition slowly deteriorated, until by the end of March, 1935, he was completely aphasic, deaf, and helpless. His legs were now in a condition of flaccid paralysis with absence of both knee and ankle-jerks. The plantar reflexes, however, remained extensor.

Death occurred on April 17, 1935.

AUTOPSY.

The body resembled that of an emaciated boy of 12 to 14 years. Numerous subcutaneous swellings, varying in size from those just visible to the naked eye up to nodules the size of half a walnut were noted on the chest, back, abdominal wall and on the right shin. Two small pigmented moles of about 5 mm. in diameter and only slightly projecting were present, one on the chest and one on the back.

Cranium: The scalp contained no tumours. The skull-cap was thin and the indentations for the meningeal vessels were noticeably deepened. The dura was not adherent to the brain and no swellings were present upon its external surface. The brain was removed only with difficulty on account of

PLATE II.

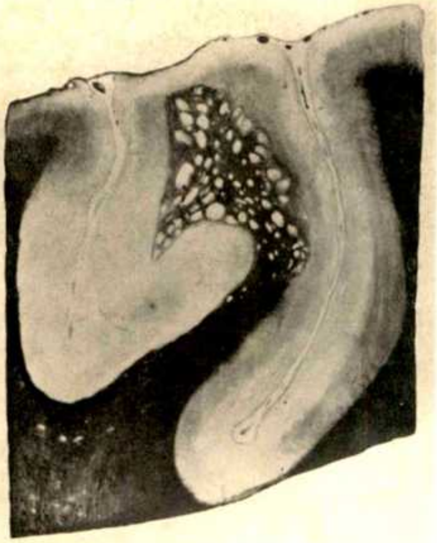

FIG. 2.

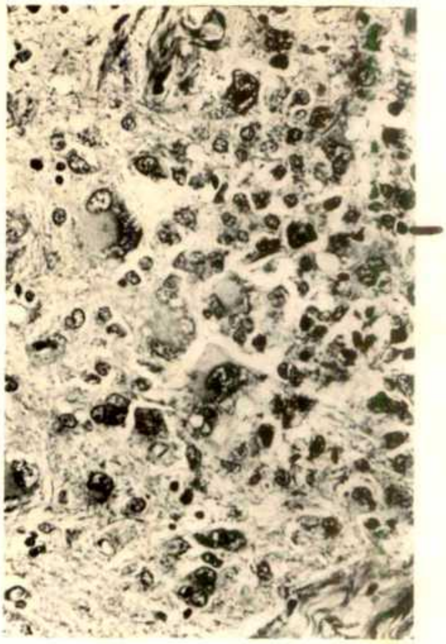

FIG. 4.

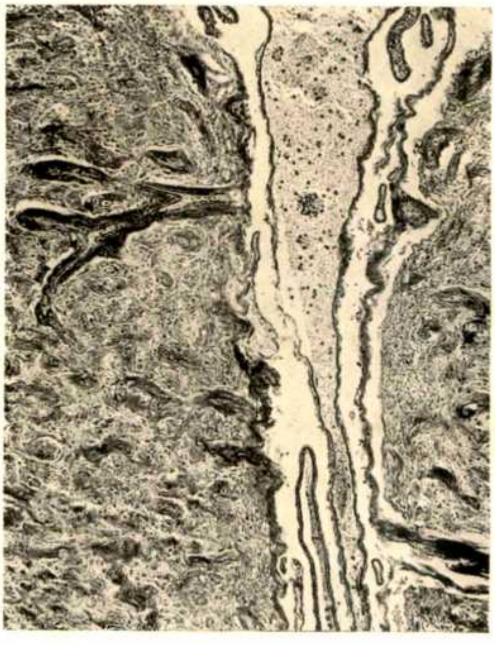

FIG. 3.

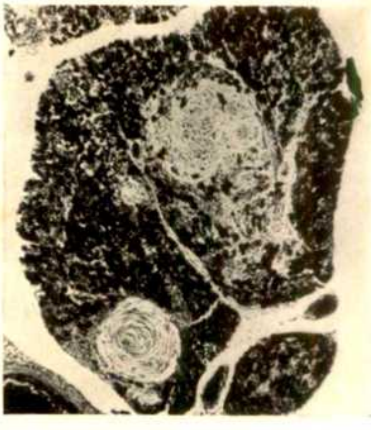

FIG. 5.

To illustrate paper by C. Worster-Drought, W. E. Carnegie Dickson, and W. H. McMenemey.

PLATE III.

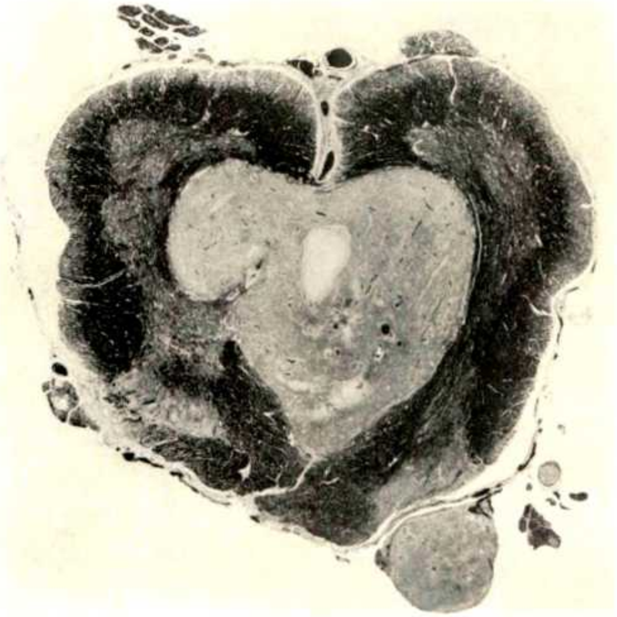

FIG. 6.

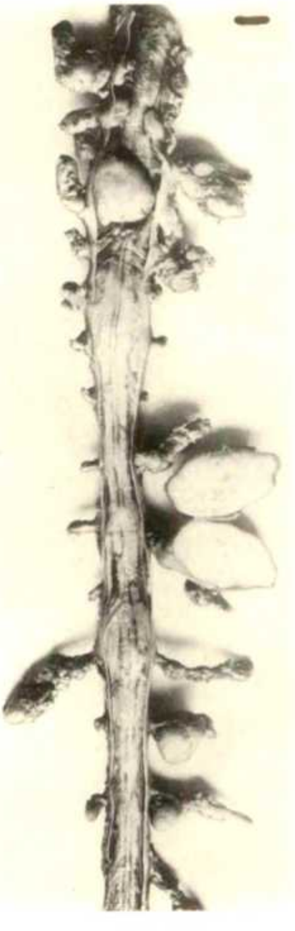

FIG. 8.

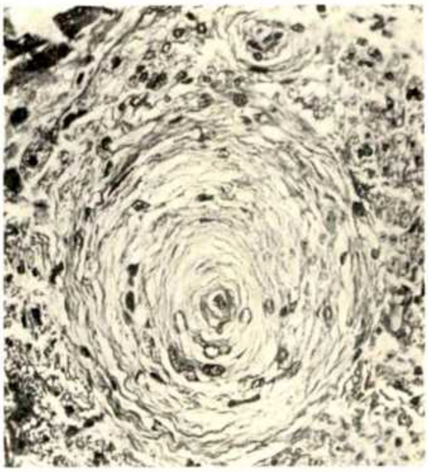

FIG. 7.

To illustrate paper by C. Worster-Drought, W. E. Carnegie Dickson, and W. H. McMenemey.

large masses which penetrated the base of the skull in relation to both auditory nerves and to the fifth nerve on the left side and extended into the petrous portion of the temporal bone on that side.

On each side of the superior longitudinal sinus the dura was adherent to the surface of the brain. On the deep aspect of the dura there were about twelve small hemispherical or ovoid flattened swellings, pale brownish-yellow in colour, with a finely granular surface and varying in size from 1 to 8 mm. in diameter; the largest was situated over the centre of the right frontal region.

Brain: This weighed 1,380 grm. Except for the comparatively slight indentations corresponding to the larger of the dural swellings the upper surface of the brain showed nothing of note. On the under surface were several swellings in relation to various cranial nerves, the largest, some 50 mm. in diameter, being at the right cerebello-pontine angle. The tumour was greyish in colour, slightly elastic to the touch and had a nodulated surface. On section, it was seen to consist mainly of a degenerate mass of semi-translucent dark grey material. A smaller tumour, about 18 mm. in diameter, was present at the left cerebello-pontine angle on the auditory nerve. It was irregular in shape with a "cauliflower-like" surface, and was intimately fused with the subjacent dura. This tumour was considerably harder to the touch than that on the opposite side.

The optic nerves throughout their course showed no swellings and appeared normal. On the left 3rd nerve was a tumour about the size and shape of an orange pip, and a similar though smaller tumour in the corresponding position on the right 3rd nerve. Numerous smaller swellings were present on the 10th 11th and 12th nerves of both sides, and on the left side two rather larger tumours probably also connected with those nerves. The tonsils of the cerebellum showed a well-marked pressure cone and the floor of the third ventricle was ballooned.

On horizontal section of the brain at the level of the pineal body, the third and lateral ventricles were found to be dilated and both foramina of Monro were considerably wider than normal. No ependymal granulations were present.

Spinal cord and nerve roots: Numerous tumours were present both upon the spinal nerve roots and within the spinal meninges (fig. 8). The largest of the latter was situated anteriorly and immediately above the level of the cervical enlargement. In shape, it resembled a flattened pebble, 17 to 18 mm. in diameter: it was attached in part to both dura and pia-arachnoid, and compressed and indented the spinal cord (fig. 9).

Many of the anterior and posterior spinal nerve roots, especially the latter, showed numerous small tumours, as many as a dozen upon a single root. Some of the nodules were only just visible to the naked eye, but most of them were about the size of a hemp seed, while others reached a diameter of 6 to 7 mm. On some of the posterior roots the tumours had developed at or near the posterior root ganglion; the largest of these was about the size of a broad bean. Although several of them projected into the intervertebral foramina, none presented the typical dumb-bell shape often seen in spinal neurofibromata. The cauda equina contained numerous small tumours, but the filum terminale was free.

The spinal dura varied much in thickness over different parts of the cord, being stretched and thinned over the larger tumours and definitely thickened in other parts. On the posterior surface of the cord in the mid-dorsal region was a localized collection of cerebrospinal fluid shut off by adhesions. On section the cord seemed severely compressed in places by the tumours.

Peripheral nerves: Tumours visible to the naked eye and varying in size from that of a hemp seed to that of a broad bean were present upon the cords of the left brachial plexus, the right 8th and 9th intercostal nerves, the left sciatic nerve, the right genito-crural nerve, and upon the right external cutaneous nerve of the thigh. The chain of swellings down the anterior aspect of the right leg was found on dissection to be superficial to the periosteum and apparently attached to a small superficial subcutaneous and not a periosteal nerve.

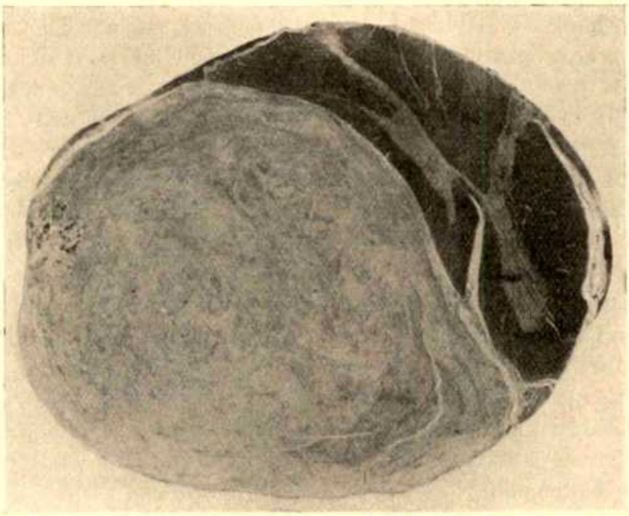

FIG. 9.—*Case* II. A low power magnification of the tumour compressing and distorting the cord in the cervical region. A small group of calcified psammomatous particles is visible near the distal edge of the tumour. (Celloidin section, Weigert-Pal. × 6.)

Other organs: Three tumours about the size of walnuts were lying in the mesentery. The lungs showed a patchy bronchopneumonic consolidation, particularly in the lower lobes, with purulent bronchitis and areas of collapse. The heart was small, its muscle pale and the valves healthy. The liver, spleen, pancreas, suprarenals and gastro-intestinal tract presented no unusual features, and there was no enlargement of lymph-nodes. No thymus was found. The thyroid body was normal in appearance, but the testes were small and undeveloped. There were no periosteal swellings. In neither of our cases were there any of Masson's paronychial or "neuromyo-arterial glomus" tumours arising from the nail-bed, a series of which has been recently published by Purdy Stout (1935).

HISTOLOGY.

Cerebello-pontine angle tumours.—Sections of the left cerebello-pontine angle tumour showed a variable degree of cellularity, a mixture of "whorls" and "palisading," the mixed feature already noted in Case I. Thin-walled vascular channels, sometimes distended with blood, occurred but were infrequent. Degenerative changes were not in evidence, but some degree of patchy œdema was noted. That part of the tumour adherent to the dura was a true "psammoma" with numerous and typical calcified particles each containing a central vessel or its remains undergoing hyaline degeneration. The intervening fibromatous cells, arranged in wisps and bundles and not infrequently in the characteristic parallel groups, were elongated and spindle-shaped; their diameters varied, but on the whole were narrow, giving them a wire-like appearance. In some parts the tissue was œdematous and in other areas hyaline degenerative changes had supervened.

The right cerebello-pontine angle tumour had undergone more extensive degenerative changes and was largely replaced by a "pseudocyst" containing semi-opaque amorphous and homogeneous dark gray material. The surviving peripheral tumour-tissue showed both varieties of cell arrangement with a varying degree of hyaline degeneration and œdema. No psammomatous particles and no hyaline vessels, such as were found in the corresponding tumour of the opposite side, were identified in the whorls. The central degenerated area consisted merely of amorphous and granular débris, enclosed within a delicate reticulum in which were scattered a few degenerating cell-nuclei. Vessels were very scanty.

With van Gieson's stain the cell bodies of both cerebello-pontine angle tumours showed the characteristic "terra-cotta" colour.

Gasserian ganglion.—On the left side this ganglion was adherent to the friable mass of growth arising from the 5th cranial nerve. Although no actual tumours were present in the Gasserian ganglion, there appeared to be in it some change analogous to tumour-formation. Proliferating cells formed small whorls around individual ganglion cells which were in varying stages of degeneration and disappearance.

Meningeal tumours.—The tumours arising from the arachnoid surface of the dura mater of the brain and cord were of meningiomatous type and were usually definitely psammomatous.

Cerebral cortex.—Histological examination of representative portions of the cerebral cortex failed to show any of the "meningio-angiomatosis" observed in Case I, nor did preparations impregnated by Cajal's gold sublimate method demonstrate any increase of astrocytes. Many of the smaller pial veins showed terminal septic thrombosis.

The choroid plexuses had undergone advanced "psammomatous" degeneration and resembled the changes seen in senility.

Spinal cord.—Many of the spinal cord tumours were "psammomatous" meningiomata and showed extensive hyaline degeneration and early calcification. In van Gieson stained preparations these meningiomatous tumours had not the terra-cotta colour characteristic of the acoustic neurofibroma. There was a possibility that some of them had arisen from posterior root ganglia, but many had developed from the inner or arachnoid aspect of the spinal dura. The majority, however, had originated from the anterior and posterior roots. Some of these tumours, especially those arising in close proximity to the cord itself, were of mixed type. In spite of extreme compression and distortion of the cord in many places, there was, as seen in Weigert-Pal preparations, remarkably little demyelination, as was also noted by Maas in his case of central neurofibromatosis.

Sympathetic ganglia.—No tumours were found on histological examination of the semilunar and other ganglia.

Sciatic nerves.—The right sciatic nerve showed no naked eye tumours, but when representative sections were examined microscopically, numerous minute tumours varying in diameter up to 1 mm. were found within it. These were moderately cellular, with a concentric laminated structure suggestive of that seen in some sensory nerve endings such as Pacinian touch corpuscles.

Pituitary body.—This organ was small, compressed and congested. Sections stained differentially showed the basophil, eosinophil and chromophobe cells in their usual and normal proportions.

Suprarenal bodies.—Except for slight congestion, these organs were normal, no neoplastic process being found in the medulla.

Mesenteric tumours.—These were neurofibromata containing both palisading and whorls, the former predominating.

Tumours in other parts.—The tumours arising from the left brachial and right lumbar plexuses, certain of the intercostal nerves, vagus nerves and the subcutaneous tumour of the abdominal wall, were all of essentially the same neurofibromatous type.

DISCUSSION.

Ætiology.—Until comparatively recently no definite hypothesis could be put forward to account for the occurrence of multiple tumour syndromes. In 1931, Lindau in his paper on cerebellar cysts and their relation to angiomatosis of the retina (von Hippel's disease), referred to the angiomata and gliomata found in the walls of these cysts, and to their association with other congenital abnormalities often of a neoplastic nature. Some 20 per cent. of these cases are familial, and Lindau suggested that the syndrome which bears his name comes into the same category as tuberous sclerosis, and ascribed it to a loss of balance in the development of the mesoderm, beginning as early as the third month of embryonic life.

For some years past we have been of opinion that there is a distinct relationship between a number of these syndromes characterized by multiple tumour formation, including not only Lindau's disease and tuberous sclerosis, but also neurofibromatosis and its variants, as well as the conditions associated with it, which we have enumerated and described in the present paper. We also include as analogous conditions a number of other multiple neoplastic syndromes, for example, myxochondro-adenoma of the base of the skull associated with cavernous angioma of the brain. A series of such multiple tumours from our hospital collection was demonstrated at the Dublin Meeting of the British Medical Association in 1933 (Carnegie Dickson); and Professor H. Bergstrand of Stockholm (1935), writing on "Sturge-Weber's Disease," which is characterized clinically by idiocy, paresis, epilepsy and visual disorders, and pathologically by cerebral hypoplasia and hypogyria, cortical calcifications, telangiectases of the pial vessels, buphthalmos and nævus flammeus of the face and other parts of the body, pointed out that these cases also come into the group now under discussion, and that incomplete variants, or *formes frustes*, of any of these may be found.

The application of recent work in Experimental Embryology, especially what has been termed "embryonic induction," throws considerable light upon the nature and origin of this group of multiple neoplastic diseases, the recent experimental work of Needham, Waddington and their colleagues being of special interest. The discovery by Spemann in 1918 that there is in the gastrula stage of the developing embryo an "organization centre" in the dorsal lip of the blastopore, the function of which is to stimulate the ectoderm of the embryo to give rise to the neural plate with its neural groove (becoming the neural canal), the notochord and the somites, was the fundamental experimental discovery upon which this new science has been founded. It has now been shown that the ectoderm of the area pellucida must be "competent" to react to this stimulus, and that the experimental implantation, say in the flank of the developing embryo, of a fragment of tissue containing living cells from this evocator centre can induce or evoke the development of a secondary or "parasitic" neural axis. Not only so, but a similar development can be induced by implanting the cells previously killed by boiling, or even by the use of an ethereal extract of them, the chemical substance involved being apparently of the nature of a sterol, i.e. a member of the chemical group which includes the antirachitic vitamins, the male and female sex-hormones, as well as œstrogenic, carcinogenic and other important stimulating or activating substances.

This extract from the dorsal lip of the blastopore is regarded as an organizer of the *first* grade, the function of which is to evoke the production of the primary axis of the embryo. There are also *secondary* evocators, which stimulate the formation of definite portions or "fields" of the embryo, e.g. a limb, an organ or part of an organ. Thus, as the optic cup grows out from the brain-vesicle and approaches the ectoderm, it induces in it the production of the lens of the eye. Similarly, the tympanic cartilage-ring stimulates the formation of the ear-drum. It has further been shown that the artificial implantation of eye-cup or cartilage—a fragment of any body cartilage will do equally well—will stimulate the production of eye-lens and ear-drum respectively in abnormal situations in the ectoderm, provided these latter are "competent," i.e. still possess sufficient formative capacity to show an active response. In other words, the tissue cells to be affected must also remain sufficiently "primitive," and must not have become too differentiated or "set" to respond to the appropriate stimulus. There is, in fact, what Needham calls a whole "hierarchy of organizers or morphogenetic hormones," of first, second, third and later order, coming into play one after the other as development advances, which stimulate and regulate the growth of tissues and organs.

It has also been discovered that these evocator substances exist, not merely in the region of the blastopore, but all over the egg, though in masked or inactive form, and may be freed and brought into play by being boiled and extracted, and then implanted in some "competent" part of the body of the developing embryo. Extracts not only of embryonic but also of adult tissues, such as mammalian liver, contain the needful sterol-like compounds and can act as evocators, some of them, however, apparently requiring to be activated by the presence or addition of nucleic, oleic or other higher fatty acid.

From this series of experiments it is but a step further to produce not normal, but pathological, forms of growth. Different parts of an organizer of the second or third order induce the formation of different organs, i.e. possess "individuating" properties which are related to the general plan of the whole body or the complete "individuation field" of the embryo. It is important also to discover how far this tendency persists in extra-uterine life and under what, if any, circumstances it may become perverted and pathological. Certain of the lower animals possess marked powers of repair, i.e. can bring these into play over an extensive "individuation field." A newt can regrow its tail, or a crab its claw or leg, but in man the powers of repair are relatively much more restricted, though in the instance of, say, the erythroblastic or leucoblastic functions of the bone-marrow, very great expansion of this capacity is possible on the appropriate stimulation of the formative cells.

In the frog it has been proved that "over-ripeness" of the ova, i.e. if they are kept for a longer period than usual before they are fertilized, will cause many of them to give rise to the production of double monsters, or if kept longer still, to teratomatous tumours, which may be actively proliferative and often definitely malignant in character. This over-ripeness involves a disturbance of the metabolism of the sterols, and the development of secondary or parasitic embryos may be induced in the flanks or belly of the primary embryo just as they were by experimental implantation of evocator substances. Over-ripeness evidently acts in the same way as boiling, and liberates these substances indiscriminately. Under this stimulation the ectoderm may become thickened and undergo epitheliomatous development. In embryos in which the cerebral vesicles have already appeared, there may be various disturbances of second-grade induction, leading to deficiencies or malformations or to the production of tumour-like masses.

Needham points out that, with ova which under optimum conditions would produce, say 90 per cent. males, the first effects of "over-ripeness" are deviations in the sex-hormones: next the uncontrolled liberation of the evocators and the production of monsters or terata, and lastly the production of a carcinogenic agent and the development of teratomata—tumours in which malignancy in varying degree may supervene, the cells escaping as it were from the control of the "individuation field" and running wild as epithelioma or sarcoma. The production of teratomatous and teratoid tumours may be explained in Needham's phrase by "the possible permutations and combinations of irresponsible organizers and perversely competent tissues"; and he states it as his belief that "all further progress in unravelling these phenomena will depend upon our knowledge of the sterols."

Our present purpose has been to discuss whether these hypotheses may be applied to the elucidation of the problems involved in the multiple neoplastic syndromes, and we suggest that the manifold aberrent processes which we have described as occurring in our two cases may well be regarded as due to certain of these "permutations and combinations."

The evocators concerned in calling forth the formation of the covering and supporting framework of the nervous system are obviously the essential nervous elements themselves, the nerve-cells with their cell-bodies and processes, more particularly the neuraxis-cylinder process itself, the nerve-fibre. These call forth a *parallel* arrangement of the cells of the nerve-sheaths whether derived as the lemmal cells from the neural crest and therefore of the nature of the peripheral glia, or from the neighbouring mesoblast as the connective-tissue cells of the epineurium investing the whole nerve-bundle.

Certain sensory nerve-terminals call forth around them the concentric whorls of Pacinian, Herbst and other forms of touch-corpuscles, the onion-like capsular tunics of which are formed by expansions of the connective tissue lamellæ of the perineurium or sheath of Henle.

These two sets of normal processes may become pathological, either because of some subtle change in the evocating nerve-elements, or from some perversion of the evocation field, mesoblastic connective tissue or glia as the case may be. The analogous palisades and concentric whorls of neurofibromatous and meningiomatous tumours, imitating the parallel structure of the supporting tissue of nerve-sheaths and the concentric capsules of touch-corpuscles respectively may be called forth by some chemical stimulus of perverted metabolism corresponding to the stimulus of sterol-containing boiled tissue or its ethereal extract, or the over-ripeness of ova. A point in favour of this argument is that the nerve-elements themselves—cells and fibres—are usually *absent* from the interior of these meningiomatous and neurofibromatous tumours.

Again the evocator may belong to the vascular system, and call forth the concentric psammomatous structure around the central choroidal capillary or around the arachnoidal villus in the meninges.

One need not elaborate the endless applications of this hypothesis. We may sum them up, as regards the multiple lesions of these neoplastic syndromes, as tissue-districts run wild, either because of some perversion in themselves or under the stimulus of some abnormal set of evocators, or perhaps to a varying combination of these two sets of factors—the details of the local lesions being brought about by the inherent tendencies of the tissues to carry out the original structural plans as component covering and supporting tissues of the nervous system.

As regards the hereditary factor, no positive family history was obtained in either of our cases. It is a well-established fact, however, that the disease is not infrequently both hereditary and familial (Preiser and Davenport, Christophe, Generisch, Minski, Cockayne, and Roger and Alliez).

The two cases here recorded appear to be of the same type as the case described by Wishart in 1822. One may regard them as being examples of a mixed type of "fibroblastomatosis," the incidence of the neoplastic process being both meningeal and perineural.

It is not possible to differentiate this syndrome clinically from "central neurofibromatosis" ("central von Recklinghausen's disease"), unless it is possible to obtain biopsy specimens, as in Kernohan and Parker's case and in the first of our own two patients.

Other examples of the association of multiple meningeal and perineural tumours have been described by Soyka (1877), Langdon (1895), Henneberg and Koch (1903), Fraenkel and Hunt (1903), Kaulbach (1906), Westphal (1908), Verocay (1910), Leischner (1910), Christin and Naville (1920), Symonds (1921), Firket (1926), Hosoi (1930), Kernohan and Parker (1932), Katzenstein (1932), and by Shapland and Greenfield (1935).

In all of these the intracranial meningeal tumours were multiple. In the cases of Biggs (1909), Fleming and Cookson (1925) and Minski (1932), there was only one tumour attached to the cranial dura in each instance. In Regnier, Dechaume, Bourrat and Lesbros' case (1927) there were two meningeal tumours in association with those of the cranial nerves. Of Funkenstein's (1904) examples, Case 1 had bilateral acoustic nerve tumours, multiple neurofibromata, a "psammoma" and an "osteo-psammoma" of the spinal dura; whilst Case 3 had one acoustic tumour and one "psammosarkoma" of the dura. Flick's patient (1928) had numerous meningeal tumours and in addition a small mass in the left internal auditory meatus, and another, the size of a cherry-stone, on the left trigeminal nerve, both probably neurofibromata.

Multiple meningeal tumours, not associated with cranial nerve tumours, have been described by Schultze (1880)—only one of which was cranial, Schmidt (1902)—two cases, Henschen (1910), Heuer and Dandy (1916), Krivy (1926), Savy (1927), and Caspar (1927)—three cases. Cestan's patient (1903), on the other hand, had multiple cranial nerve tumours only.

Many but not all of the above have been associated with "peripheral neurofibromatosis" (von Recklinghausen's disease) of greater or lesser degree.

Acoustic nerve tumours in association with peripheral neurofibromata and neurofibromata of the cord in association with the peripheral disease, on the other hand, are relatively frequent in their occurrence and constitute the majority of cases of "central neurofibromatosis."

That we are dealing with variants of one disease has long been apparent, and Cornil (1933) has suggested the name "neuroectodermomatosis." This term has found favour with Roger and Alliez (1934), Agostini (1934) and others.

The nature of peripheral neurofibromatosis.—Although this condition (so-called "von Recklinghausen's disease") had been known for many years prior to the classical description in 1882 by von Recklinghausen himself, and had been admirably described and illustrated by Tilesius in 1793 and by Walther in 1814, it was not until some years later that an attempt was made to investigate the nature of the swellings. According to R. W. Smith, whose well-illustrated folio book (1849) may be consulted by those interested in the history of the subject, the term "neuroma" was introduced by Odier in 1803 to apply to a "tumour connected with nerve." Barkow (1829) was one of the first to recognize the importance of differentiating the case with solitary tumour from that suffering from the generalized disease; and Knoblauch (1844) went a step further in suggesting that the generalized disease resulted from "an original vice of conformation" and had no relation to the occurrence of solitary tumours. Smith (1849) and Virchow (1858) continued to term the tumour "neuroma," although the latter author realized that the majority were false or pseudo-neuromata. Von Recklinghausen (1882) considered these peripheral nerve tumours to be of fibrous tissue origin, an opinion which was shared later by Alexis Thompson (1900). Of the word "neuroma" it is interesting to recall that the latter said: "It is a convenient term, and employed in the clinical sense it indicates the most important feature of any particular tumour, viz. its seat in a nerve, irrespective altogether of its structure."

In 1910 the term "neurinoma" was introduced by Verocay to cover all the nerve tumours, both peripheral and central, in his case of the syndrome of Wishart. He considered that they arose from undifferentiated neurocytes which were normally capable of giving rise to sheath, ganglion and glial cells and under pathological conditions of growth could produce the corresponding type of tumour.

Valuable contributions to the histology of these tumours have been made by Durante, Antoni and by Penfield. The latter concludes that the presence of nerve fibrils within the tumours may be pathognomonic of neurofibromata, and that in this respect they differ from true "perineurial fibroblastomata." It would perhaps avoid confusion if we regarded the former as merely a more differentiated type of the latter.

The term "neur*in*oma"[1] has come to be applied only to the "solitary" type of nerve sheath tumour, but its use in this respect has been criticized by Stout (1935) on the grounds that it implies a nerve *fibre* tumour. He also dismisses the term "perineurial fibroblastoma" introduced by Penfield, and the two other popular alternatives "Schwannoma" and "peripheral glioma" as unsuitable. Stout suggests that this type of tumour be known as "neurilemoma." This word certainly has the advantage of terminological precision and does not attempt to do more than suggest the site of origin of the tumour.

In "peripheral neurofibromatosis," however, the tumours are nearly always incompletely differentiated and consequently fall strictly into the category of fibroblastomata. It seems certain that they can arise from the endoneurium, the epineurium, also presumably from the sheath of Schwann (the supposed origin of the solitary tumour) and the perineurium. In other words, they can theoretically, and often do, arise from any or all of the tissue elements connected with the nerves. They are, therefore, "perineural fibroblastomata" (not perineurial, a term which suggests an origin only in the perineurium).

The nature of acoustic nerve tumours.—Acoustic nerve tumours may be unilateral or bilateral, and may or may not be associated with other manifestations of "neurofibromatosis"—central, peripheral or a combination of both.

Minski (1932) concludes that bilateral acoustic nerve tumours with generalized peripheral neurofibromatosis are much more frequent than bilateral acoustic tumours alone, there being records of thirty-seven cases of the former syndrome and only seven of the latter. It would also seem that if acoustic tumours are associated with peripheral neurofibromatosis, the former are almost always bilateral. This is of interest, because it is stated by Cushing (1917) that for every case of bilateral acoustic nerve tumour (presumably uncomplicated by peripheral neurofibromatosis) there are 100 cases of unilateral tumour.

Acoustic nerve tumours were considered by Sternberg (1900) to be derived from an "anlage" of glial tissue. Cushing (1917) remarked on their similarity to the peripheral nerve tumours, noting that they differed only in their greater tendency to the formation of glia-like areas and in the absence or extreme rarity within them of nerve-fibres either with or without a myelin sheath. He considered that acoustic nerve tumours arose from undifferentiated cells at the junction of the glial elements with the sheath of Schwann. Skinner (1929), however, showed that the type-cell of the acoustic nerve tumour was the neurilemma-sheath cell, and he gave reasons for the belief that these cells exist in unusual numbers in the vestibular portion of the nerve, a view shared by Gardner and Frazier (1930). Penfield believes in their fibroblastomatous origin and emphasizes the importance of the identification of collagen fibrils in these tumours. The acoustic nerve tumours found in association with peripheral neurofibromatosis he considers to be of a different order, the presence of nerve-fibres within them being pathognomonic of neurofibromata and not of fibroblastomata, and he maintains that these fibres are found in cases of bilateral familial acoustic nerve tumours as well as in association with peripheral neurofibromatosis. Minski, however, was unable to demonstrate nerve-fibres in his case of bilateral familial acoustic nerve tumour, and similarly we have been unable to find them in our two cases except at the surface of the tumours, where they are obviously merely surviving fibrils of the original acoustic nerve. We ourselves are of opinion that acoustic nerve tumours, whether they occur singly, bilaterally or in association with peripheral or central neurofibromatosis, allowing for slight individual differences, are essentially similar in structure and of the nature of neurofibroblastomata.

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[1] *Note.*—Neurinoma = Neur-in-oma. The Greek word *νεῦρον* meant originally a sinew or tendon; in the plural it came metaphorically to mean strength, *vreo* "nerves"; later it was applied to the fibres of plants; but not until Galen's time was it used to denote the physical nerves themselves (Liddell and Scott). The word *ἶς*, *ἰνός*, originally meant a muscle (at the back of the neck, *cf.* "*ἰνίον*"), and later came to mean a "fibre." The term "Inoma" was introduced by Paget for "Fibroma." "Neur*in*oma" therefore means a nerve-*fibre*-tumour.

† *Λέμμα*, a skin or sheath which can be peeled off (*λέπω* to strip or peel). Dr. Stout informs us that he believes it to be correct to spell this word with the single "m."

The nature of meningeal tumours, and the association of "neurofibromatosis" with glioma.—The great majority of meningeal tumours occur singly, but, as has already been stated, instances in which they are multiple do occur, some eleven examples having been recorded. In association with peripheral and central neurofibromata, they are, however, practically always multiple, only three cases in which they are single having been described.

The term "meningioma" has been popularized by Cushing and Percival Bailey as being non-committal, for there is still considerable difference of opinion as to the exact histogenesis of these tumours. Some authors—Schmidt, Bailey, Bucy and Mallory—regard them as arising from clusters of arachnoidal cells. The view that they are fibroblastomata affords a satisfactory explanation of the variety of histological pictures which may be found. Cushing's view, however, is that the meningoblasts are capable of differentiating into angioblasts, fibroblasts, and possibly other types of cell; the "meningio-angiomatosis" described in our first case appears to confirm this opinion.

Diffuse forms of meningeal tumour and "sarcomatous" changes were noted by Nonne (1902), Markus (1913), Bassoe and Shields (1916), Pirie (1919), Boyd (1925), Fried (1926), Moorhead and Wigham (1926), Connor and Cushing (1927), Bailey (1929), Learmonth (1929), by Froment, Dechaume and Christy (1930) and by A. H. Jackson (1933). Froment, Dechaume and Christy refer to the diffuse meningeal growths under the name of "Maladie d'Ollivier" (1825). Boyd noted tumour cells spreading along the perivascular prolongations of the subarachnoid space, and is of the opinion that the great majority of cases are secondary to neoplastic processes elsewhere. Moorhead and Wigham, under the term "meningitis carcinomatosa," described a diffuse endothelial growth over the cerebral cortex and the cerebellum, but they were unable to find a primary growth, permission for the examination of the viscera not having been granted. There is little doubt that many of the diffuse forms of growth are either metastatic and often carcinomatous in nature or are spreading medulloblastomata; nevertheless, there remains a proportion of cases which are probably of primary meningeal origin. Craig (1927) drew attention to the fact that intracranial endothelioma (i.e. what is now known as "meningioma") is not always benign, and Hosoi was able to collect sixty-five cases of "sarcomatous" degeneration of such meningeal tumours. Bailey made an interesting study of eight cases of intracranial sarcomatous tumours of the leptomeninges, all of different type, seven of which were apparently primary. Bailey and Bucy classified meningeal tumours into nine separate groups—mesenchymal, angioblastic, meningotheliomatous, psammomatous, osteoblastic, fibroblastic, melanoblastic, sarcomatous and lipomatous. Towne (1926) described invasion of the inferior longitudinal sinus by a meningioma of the falx cerebri, the process spreading into other venous sinuses; and we note the occurrence of multiple small meningiomata projecting into the superior sagittal sinus in our first case. Connor and Cushing (1927) described two cases—a male of 63 years, with a diffuse basal endotheliomatosis with tumour-cells originating from the adventitial sheath of blood-vessels; and a male of 11 years, with a surface gliomatosis, the cells being of the undifferentiated type as seen in a medulloblastoma.

Examples of the occurrence of gliomata in association with neurofibromatosis have been collected by Strube (1898), Patoir and Raviart (1901), Henneberg and Koch (1903), Hulst (1904), Kaulbach (1906), Verocay (1910), Schnyder (1928), Dupouy, Courtois and Pichard (1929), Roger and Cremieux (1929), Stewart and Copeland (1931), and by Shapland and Greenfield (1935). Also, central tumours—the nature of which it was not possible to determine owing to the absence of post-mortem examination—have recently been reported in association with neurofibromatosis by Else (1933), Carrillo (1934) and Kanaar (1934). They are usually cerebral in origin, and Bailey states that they are frequently of the nature of polar spongioblastomata. We have recently seen an example of this type of tumour situated in the basal ganglia in a case of peripheral neurofibromatosis.

In a recent case of Roger and Alliez (1934), however, the cerebral tumour associated with peripheral neurofibomatosis was a glioblastoma multiforme. These writers also describe a case of diffuse meningeal gliomatosis resembling a medulloblastoma in a member of a family suffering from neurofibromatosis. Also, Foerster and Gagel (1934) described a "central diffuse Schwannosis" in association with this disease, the cells not being characteristic of spongioblasts, ependyma or microglia, but rather of sheath-cells. Martz (1933) noted a gliomatosis of the brain, spinal cord and pituitary body in a case of neurofibromatosis involving principally sympathetic ganglia, and Barber and Shaw (1922) have described the occurrence of a pituitary tumour.

That the peripheral nerve-tumours are capable of becoming malignant has been recognized for some time and Williams (1933) has reported a case of neurofibromatosis in which a "fibroma" of the sciatic nerve was removed and "recurred" as a spindle-celled sarcoma.

Generalized neurofibromatosis. — Penfield believes that "multiple neurofibromatosis" is a generalized fibrous connective tissue reaction involving both nerve-fibres and connective-tissue elements, the multiple manifestations depending upon the local cellular reaction peculiar to the tissue from which the tumour arises.

We are led to believe that this view is correct as far as it implicates the supporting tissue and that neurofibromatosis, both central and peripheral, is in part a dysplasia of the supporting tissue of the entire nervous system, both central and peripheral, but we are doubtful as to whether the nerve-elements themselves necessarily participate in the neoplastic formation. In the consideration of such tumours, we have found Adami's classification helpful, as it obviates the supposed difficulty of grouping together "pulp" or supporting tissue tumours derived from any of the three embryonic layers. The term "Neurofibroblastomatosis"—or "Fibroblastomatosis of the nervous system"—covers all the numerous manifestations of the disease. We suggest, therefore, that until more is known of the subject, von Recklinghausen's disease should be considered pathologically as a neurofibroblastomatosis.

As the majority of the tumours are on nerves or meninges, the following classification of the main varieties of the disease may be formulated. It should be remembered, however, that glial tumours may complicate all varieties of the disease.

Main varieties of neurofibroblastomatosis.—A. Central Type: (1) Meningeal and Perineural—Syndrome of Wishart (1822)—rare. (2) Meningeal only—Syndrome of Schultze (1880)—rarest. (3) Perineural only—Syndrome of Knoblauch (1843)—commonest. B. Peripheral type: Peripheral neurofibromatosis or von Recklinghausen's disease (1882) first described by Tilesius in 1793.

Types A and B are not infrequently combined. There are many subvarieties of (1) and (3) of Type A, but it serves no useful purpose further to subdivide them.

Any of these types may be associated with a greater or lesser degree of malignancy in their individual tumours, and this is a further reason for regarding them as variants of one disease—neurofibroblastomatosis.

In addition there are other and allied pathological processes with which the condition may be associated.

The association with and relation to syringomyelia.—Several authors have noted the occurrence of a syringomyelic cavitation of the spinal cord in association with neurofibromatosis, viz. Patoir and Raviart (1901), Castronuovo (1920), and Kernohan and Parker (1932). Katzenstein (1932) has reported an ependymal reaction and hydromyelia.

In both our examples there was in the spinal cord cavitation and an ependymal reaction, most marked in Case I. Such cavitation may be a secondary phenomenon due to compression and distortion of the cord and to the impoverished blood-supply. On the other hand, since syringomyelia itself is a disease of presumably similar developmental origin, it is natural to regard the association as not merely fortuitous. In this connection it is interesting to note that acromegaloid tendencies have been described in both diseases. We can find no record, on the other hand, of the clinical entity known as "syringomyelia" being complicated by neurofibromatosis, either peripheral or central. It would seem best for the present, therefore, to regard the question of the possible relationship of the two diseases as unsettled.

The association with and relation to tuberous sclerosis.—This disease has been fully described, within recent years, by Critchley and Earl (1932). Orzechowski and Nowicki (1912) recorded the case of a male, aged 18, with the typical post-mortem findings of tuberous sclerosis, combined with many of the features of peripheral and central neurofibromatosis. Other authors have described similar associations (Gamper, Urbach and Wiedman, and Rump), and in a review of the subject Critchley is in favour of regarding the two diseases as closely related, a view also put forward by one of us (W. E. C. D., 1933).

In connection with the investigation of our two cases, we wish to express our thanks for the skilled technical assistance given us by Messrs. John Ottewill and Charles Martin.

SUMMARY.

(1) Two cases are recorded of multiple tumours of the nervous system—meningeal and perineural—with associated and analogous changes in glia and ependyma.

(2) The clinical manifestations consisted of multiple cranial nerve lesions, including bilateral nerve deafness, ocular palsies, nystagmus and papillœdema; speech difficulties; a combination of upper and lower motor neurone paresis of the limbs and bilateral pes cavus. In one case subcutaneous neurofibromata were numerous, but in the other only one such tumour—on the back—appeared. The cerebrospinal fluid of both cases showed Froin's syndrome. The disease in the first case lasted eight years, and in the second one year and eight months.

(3) Histologically, the tumours varied from frank meningioma to typical neurofibroma, depending upon the site of origin, those arising from meninges tending to be psammomatous, those from nerve-sheaths neurofibromatous. Admixtures of the two types occurred in areas where a double origin was possible, e.g. the cerebello-pontine angle tumours and certain of those arising in relation to the spinal cord. Analogous changes in the glia and ependyma, and also syringomyelic cavitation were present in the spinal cords of both cases.

(4) The association of multiple meningeal and perineural tumours is infrequent and was first described by Wishart in 1822. This "Syndrome of Wishart" is one variety of "neurofibromatosis."

(5) The disease from the pathological standpoint might more accurately be described as "neurofibroblastomatosis." The term "von Recklinghausen's disease" should be confined to the purely peripheral subcutaneous form of the disease.

(6) The probable bearing of recent experimental work in inductive embryology upon the general problem of multiple neoplastic syndromes is discussed.

(7) A clinical classification of the different forms of "neurofibroblastomatosis" is suggested and an account of the pathological variants is given.

REFERENCES.

ADAMI, J. "On the Classification of Tumours," *Journ. Path. and Bact.*, 1902-03, **8**, 243.

AGOSTINI, C. "Sui rapporti tra la gliomatosi centrale e quella periferica in riferimento alla dottrina delle neuro-ecto-dermosi," *Riforma med.*, 1934, **50**, 1679-1685.

ANTONI, N. R. E. "Ueber Rückenmarkstumoren und Neurofibroma." Munich, 1920.

BAILEY, P. "Intracranial Sarcomatous Tumors of Leptomeningeal Origin," *Arch. Surg.*, 1929, **18**, 1359.

BAILEY, P., and BUCY, P. C. "The Origin and Nature of Meningeal Tumors," *Amer. Journ. Cancer*, 1931, **15**, i.

BAILEY, P., CUSHING, H., and EISENHARDT, L. "Angioblastic Meningiomas," *Arch. Path. and Lab. Med.*, 1928, **6**, 953.

BARBER, H. W., and SHAW, M. "Case of von Recklinghausen's Disease with Pituitary Tumour," *Brit. Journ. Derm. and Syph.*, 1922, **34**, 207.

BARKOW. "Bemerkungen uber die Nervensanschwellungen," *Nov. Act. physic. Med.*, 1829, **14**, 2.

BASSOE, P., and SHIELDS, C. L. "Diffuse Endothelioma of the Spinal Cord," *Journ. Amer. Med. Assoc.* (Abstract), 1916, **66**, 1888.

BERGSTRAND, HILDING. "On Sturge-Weber's Disease" (Abstract). Second Internat. Neurol. Congress, London, 1935, p. 124.

Idem. "Gefassmissbildungen und Gefassgeschwulste des Gehirns." Leipzig, 1936.

BIGGS, G. N. "A Case of Multiple Intracranial Tumours with Involvement of Both Auditory Nerves," *Lancet*, 1909, **2**, 14.

BOYD, W. "Diffuse Tumors of Meninges," *Amer. Journ. Path.*, 1925, **1**, 583.

CABOT and SMITH, F. J. C. (*Case* 19162). "Multiple Neurofibromata of Acoustic Nerve, Brain, and Spinal Cord," *New England Journ. Med.*, 1933, **208**, 849.

CARRILLO, R. "Relacion entre las manifestaciones cutaneas de la enfermedad de Recklinghausen y los tumores cerebrales coexistentes," *Arch. Argent. de Neurol.*, 1934, **11**, 156.

CASPAR, T. "Beiträge zur Pathologie der multiplen und diffusen Endotheliome der Hirnhäute," *Deutsch Zeitschr. f. Nervenheilkunde*, 1927, **96**, 85.

CASTRONUOVO, G. "La neurofibromatosi diffusa (Morbo di Recklinghausen)," *Riforma med.*, 1920, **36**, 817.

CESTAN, R. "La neurofibrosarcomatose," *Rev. Neurol.*, 1903, **11**, 745.

CHESELDON, W. "The Anatomy of the Human Body." London, 1740.

CHRISTIN, E., and NAVILLE, F. "A propos de neurofibromatoses centrales," *Ann. de Méd.*, 1920, **8**, 30.

CHRISTOPHE, LOUIS. "Neurofibromatose familiale," *Journ. Belge. de Neurol. et Psych.*, 1933, **33**, 797.

COCKAYNE, E. A. "Inherited Abnormalities of the Skin and its Appendices." London, 1934, p. 274.

CONNOR, C. L., and CUSHING, H. "Diffuse Tumors of the Leptomeninges," *Arch. Path.*, 1927, **33**, 374.

CORNIL, L., KISSEL, P., BEAU, A., and ALLIEZ, J. "Les formes généralisées et dissociées de la maladie de Recklinghausen (Neuroectodermomatose) Essai de synthèse des différents types de tumeurs du système nerveux," *La Presse Méd.*, 1933, **41**, 2077.

CRAIG, W. McK. "Malignant Intracranial Endotheliomata," *Journ. Surg. Gyn. and Obstet.*, 1927, **45**, 760.

Critchley, MacD. "Tuberose Sclerosis (epiloia)," *Med. Annual*, 1933, p. 511.

Critchley, MacD., and Earl, C. T. C. "Tuberose Sclerosis and Allied Conditions," *Brain*, 1932, **55**, 311.

Cushing, H. "Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle." Philadelphia, 1917.

Idem. "Meningiomas, their Source and Favoured Sites of Origin," *Brain*, 1922, **45**, 282.

Dickson, W. E. Carnegie. "Certain Intracranial Tumours: their Variability and Multiplicity," *Brit. Med. Journ.*, 1933, **2**, 1016.

Dickson, W. E. Carnegie, and Fowler, J. S. "Tuberous (Tuberose) Sclerosis," *Quart. Journ. Med.*, 1910, **4**, 43.

Dupouy, R., Courtois and Pichard. "Schwannome cutané avec neurogliomatose meningo-encephalique," *Presse Méd.*, 1929, **37**, 1012.

Durante, J. "Nerfs," Cornil and Ranvier's "Manuel d'Anat. patholog.," 1917, **3**, 425.

Else, J. E. "Von Recklinghausen's Disease with Tumour of Spinal Cord," *Surg. Clin. North Amer.*, 1933, **13**, 25.

Firket, T. "Maladie de Recklinghausen centrale, tumeurs pontocérébelleuses bilaterales et meningiomes multiples," *Ann. d'Anat. path.*, 1926, **3**, 407.

Fleming, G. W. H. T., and Cookson, H. A. "A Case of Multiple Neurofibromata associated with a True Angioneurofibroma of the Acoustic Nerve, Jacksonian Epilepsy and Osteoporosis," *Journ. Neurol. and Psychopath.*, 1925, **6**, 104.

Flick, K. "Fehldiagnose bei multiplen Endotheliomen der Dura," *Zentralbl. f. Chir.*, 1928, **55**, 2321.

Foerster, O., and Gagel, O. "Zentrale diffuse Schwannose bei Recklinghausenscher Krankheit," *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1934, **151**, 1-16.

Fraenkel, J., and Hunt, J. R. "Tumours of the Pontomedullocerebellar Space—Acoustic Neuroma (Central Neurofibromatosis)," *Med. Record*, 1903, **64**, 1001.

Fried, B. M. "Sarcomatosis of the Brain," *Arch. Neurol. and Psych.*, 1926, **15**, 205.

Froment, J., Dechaume, J., and Christy, H. "Tumeur meningée diffuse primitive," *Lyons Méd.*, 1930, **145**, 813.

Funkenstein, O. "Ein Beitrag z. Kenntnis der Tumoren des Kleinhirnbrückenwinkels," *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1905, **14**, 157.

Gamper, E. "Zur Kenntnis der zentralen Veränderungen bei Morbus Recklinghausen," *Journ. f. Psych. u. Neurol.*, 1928, **39**, 39.

Gardner, W. J., and Frazier, C. H. "Bilateral Acoustic Neurofibromas," *Arch. Neurol. and Psychiat.*, 1930, **23**, 266.

Genersich, A. "Multiple Neurome," *Virchow's Archiv*, 1870, **49**, 15.

Greenfield, J. G. "The Pathological Examination of Forty Intracranial Neoplasms," *Brain*, 1919, **42**, 29.

Henneberg and Koch, M. "Ueber 'centrale' Neurofibromatose und die Geschwülste des Kleinhirnbrückenwinkels (Acousticneurome)," *Arch. f. Psych.*, 1903, **36**, 251.

Henschen, F. "Ueber Geschwülste der hinteren Schadelgrube insbesondere des Kleinhirnbrückenwinkels," Jena, 1910.

Heuer, G. J., and Dandy, W E. "A Report of Seventy Cases of Brain Tumour," *Bull. Johns Hopkins Hosp.*, 1916, **27**, 224.

Hosoi, K. "Meningiomas, with Special Reference to the Multiple Intracranial Type," *Amer. Journ. of Path.*, 1930, **6**, 245; and "Multiple Neurofibromatosis with Special Reference to Malignant Transformation," *Arch. Surg.*, 1931, **22**, 258.

Hulst, J. P. L. "Beitrag zur Kenntnis der Fibrosarkomatose des Nervensystems," *Virchow's Arch. f. path. Anat.*, 1904, **177**, 317.

Jackson, A. H. "Three Cases of Multiple Neurofibromatosis with Malignant Degeneration," *Journ. Nerv. and Ment. Dis.*, 1933, **78**, 581.

Kalischer, S. "Ein Fall von Telangiectasie (Angiom) des Gesichts und der weichen Hirnhaut," *Arch. f. Psych. u. Nervenheilk.*, 1901, **34**, 171.

Kanaar, A. C. "Neurofibromatosis: A Report on Three Cases," *St. Barts. Hosp. Journ.*, 1934, 210.

Katzenstein, R. "Ueber innere Recklinghausensche Krankheit (Endotheliome, Neurinome, Gliome, Gliose, Hydromyelie)," *Virchow's Arch. f. Path. Anat.*, 1932, **286**, 42.

Kaulbach, F. W. J. "Ein Fall von multiple Neurofibromatose des peripheren Nervensystems kombiniert mit Fibromen des Nervenwurzeln, Gliomen des Rückenmarks und Sarkomen der Dura Mater," Inaug. Diss., Marburg, 1906. (Quoted by Stewart and Copeland.)

Kernohan, J. W., and Parker, H. L. "A Case of von Recklinghausen's Disease, with Observations on the Associated Formation of Tumours," *Journ. Nerv. and Ment. Dis.*, 1932, **76**, 313.

Knoblauch, J. "De Neuromate et gangliis accessoriis," Inaug. Diss., 1843. Frankfurt.

Krivy, M. "Étude anatomique d'un cas de tumeurs multiples des méninges," *Rev. Neur.*, 1926, **33**, 154.

Langdon, F. W. "Multiple Tumours of the Brain; Fibrocystoma of Pons and Cerebellum and Multiple Fibropsammomata of Dura, Pia Arachnoid and Cortex Cerebri," *Brain*, 1895, **18**, 551.

Learmonth, J. R. "Meningiomas of the Spinal Cord with Extradural Spread," *Surg. Clin. North Amer.*, 1929, **9**, 979.

Leischner, H. "Zur Chirurgie der Kleinhirnbruckenwinkeltumoren," *Mitt. a. Grenzgeb. d. Med. u. Chir.*, 1911, **22**, 675.

Lindau, Arvid. (*a*) "Studien uber Kleinhirncysten, Bau, Pathogenese u. Beziehungen zur Angiomatosis Retinæ," Aus dem pathologisch-anatomischen Institut der kgl. Universität zu Lund, 1926. (*b*) "Vascular Tumours of the Brain and Spinal Cord," *Proc. Roy. Soc. Med.*, London, 1930, **23**, 363; and 1931, **24**, 1.

Maas, O. "Beitrag zur Kenntnis der Recklinghausenschen Krankheit," *Monat. f. Psych. u. Neurol.*, 1910, **28**, 167.

Markus, O. "Ein Fall von diffuser Sarkomatose der Pia Mater," *Arch. f. Psych.*, 1913, **51**, 322.

Martz, L. "Neurofibromatose des Sympathicus mit ungewöhnlicher Beteiligung des Ruckenmarks, Gehirns u. der Hypophyse," *Frankfurt. Ztschr. f. Path.*, 1933, **46**, 119.

Minski, L. "Familial Bilateral Acoustic Tumours," *Journ. Neurol. and Psychopath.*, 1932, **12**, 289.

Moorhead, T. G., and Wigham, T. J. "Meningitis Carcinomatosa," *Irish Journ. Med. Sci.*, 1926, **6**, 135.

Needham, J. "New Advances in the Chemistry and Biology of Organized Growth," *Proc. Roy. Soc. Med.*, London, 1936, **29**, 1577.

Needham, J., Waddington, C. H., and Needham, D. M. "Physico-chemical Experiments on the Amphibian Organizer," *Ibid.*, London, 1934, **27**, 893.

Nonne, M. "Ueber diffuse Sarkomatose der Pia Mater des ganzen Centralnervensystems," *Deutsch. Zeit. f. Nervenheilk.*, 1902, **21**, 396.

Odier, L. "Neuromes," "Manuel de Med. Pratique," Genevre, 1803.

Orzechowski, K., and Nowicki, W. "Zur Pathogenese u. pathologischen Anatomie der multiplen Neurofibromatose u. der Sclerosis tuberosa," *Zeit. f. d. g. Neur. u. Psych.*, 1912, **11**, 237.

Patoir, J., and Raviart, G. "Gliomes et formation cavitaire de la moelle—neurofibromes radiculaires—névrite des sciatiques," *Arch. de méd. expér. et d'anat. path.*, 1901, **13**, 93.

Penfield, W. "The Encapsulated Tumors of the Nervous System," *Journ. Surg. Gyn. and Obst.*, 1927, **45**, 178.

Idem. "Tumours of the Sheaths of the Nervous System," *Arch. Neurol. and Psych.*, 1932, **27**, 1298.

Idem. "Cytology and Pathology of the Nervous System." (Hoeber), New York, 1932, **3**, Sect. 19.

Penfield, W., and Young, A. W. "The Nature of von Recklinghausen's Disease and the Tumers Associated with it," *Arch. Neurol. and Psych.*, 1930, **23**, 320.

Pirie, J. H. H. "A Case of Diffuse Endothelioma of the Pia Arachnoid," *Med. Journ. S. Africa*, 1919, **15**, 157.

Preiser, S. A., and Davenport, C. B. "Multiple Neurofibromatosis and its Inheritance," *Amer. Journ. Med. Sci.*, 1918, **156**, 507.

von Recklinghausen, F. "Ueber die multipler Fibrome der Haut." Berlin, 1882.

Regnier, J., Dechaume, Bourrat and Lesbros. "Tumeurs méningées et Tumeurs des nerfs craniens," *Ann. d'anat. path.*, 1927, **4**, 940.

Rhoads, C. P., and van Wagener, W. P. "Observations on the Histology of the Tumours of the Nervus Acousticus," *Amer. Journ. Path.*, 1928, **4**, 145.

Roger, H., and Alliez, J. "La forme familiale et héréditaire des tumeurs cérébrales associées a la neurogliomatose cutanée," *Bull. Acad. de Med.*, Paris, 1934, **111**, 620.

Roger, H., and Cremieux, A. "Les Tumeurs cérébrales multiples," *Ann. de Med.*, 1929, **26**, 5.

Rump, C. "Ein Fall multipler Neurome," *Virchow's Arch.*, 1880, Bd. **80**, 177.

Savy, P., Dechaume, J., and Puig, R. "Gliomes ou meningoblastomes," *Lyons méd.*, 1927, **140**, 3.

Schmidt, M. B. "Ueber die Pacchionischen Granulationen und ihr Verhältniss zu den Sarkomen und Psammomen der Dura Mater," *Virchow's Arch. f. path. Anat.*, 1902, **170**, 429.

Schnyder, P. "Ueber, Gliose, Gliom und Gliomatose und ihre Beziehungen zur Neurinomatosis," *Schweiz' Arch. f. Neurol. and Psych.*, 1928, **23**, 116.

Schultze, F. "Ein Fall von eigenthümlicher multipler Geschwülstbildung des centralen Nervensystems und seiner Hüllen," *Berl. Klin. Wochenschr.*, 1880, **17**, 523.

Shapland, C. D., and Greenfield, J. G. "A Case of Neurofibromatosis with Meningeal Tumour Involving the Left Optic Nerve," *Trans. Ophthalmolog. Soc.*, 1935, **15**, 257.

Skinner, H. A. "Origin of Acoustic Nerve Tumours," *Brit. Journ. Surg.*, 1929, **15**, 440.

Smith, R. W. "A Treatise on the Pathology, Diagnosis and Treatment of Neuroma," Dublin, 1849.

Soyka, I. "Ueber den Bau und die Stellung der multiplen Neurome," *Vierteljahr Schr. f. d. pract. Heilkunde*, 1877, **135**, 1.

Sternberg, C. "Beitrag zur Kenntnis der sogenannten Geschwulste des N. acusticus," *Deut. Zeitschr. f. Nervenheilk.*, 1900, **21**, 163.

Stewart, F. W., and Copeland, M. M. "Neurogenic Sarcoma," *Amer. Journ. Cancer*, 1931, **15**, 1235.

Stout, A. P. "Tumors of the Neuromyo-Arterial Glomus," *Amer. Journ. Cancer*, 1935, **24**, 255.

Idem. "The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemoma). *Ibid.*, 1935, **24**, 751.

Strube, G. "Ueber eine Combination allgemeiner Neurofibromatose mit gliom des Rückenmarks," *Virchow's Arch. f. path. Anat.* (Suppl.), 1898, **151**, 78.

Symonds, C. P. "A Case of Bilateral 8th Nerve Tumours associated with Multiple Neurofibromata and Multiple Endotheliomata of the Meninges," *Journ. Neurol. and Psych.*, 1921, **2**, 142.

Thompson, A. "On Neuroma and Neurofibromatosis," Edinburgh, 1900 (Turnbull and Spears).

Tilesius, W. G. "Historia pathologica singularis cutis turpitudinis," Leipzig, 1793.

Towne, E. B. "Invasion of the Intracranial Venous Sinuses by Meningeoma," *Ann. Surg.*, 1926, **83**, 321.

Urbach, E., and Wiedman, A. "Morbus Pringle und Morbus Recklinghausen," *Arch. f. D. und S.*, 1929, **158**, 334.

Verocay, J. "Zur Kenntnis der Neurofibrome," *Beit. z. path. Anat. u. z. allg. Path.*, 1910, **48**, 1.

Virchow R. "Das wahre Neuron," *Arch. f. path. Anat.*, 1858, **13**, 256.

Waddington, C. H. "Experiments on Embryonic Induction," *Journ. Exper. Biology*, 1934, **11**, 211.

Walther, F. v. "Ueber die angebohrren Fetthautgeschwülste und andere Bildungsfehler," Landshut, 1814.

Weber, F. Parkes. "A Note on the Association of Extensive Hæmangiomatous Nævus of the Skin with Cerebral (Meningeal) Hæmangioma, especially cases of Facial Vascular Nævus with Contralateral Hemiplegia," *Proc. Roy. Soc. Med.*, London, 1929, **22**, 431.

WESTPHAL, A. "Beitrag z. Kenntnis der Kleinhirnbrückwinkeltumoren und der multiplen Neurofibromatose," *Deut. Zeitschr. f. Chir.*, 1908, **96**, 408.

WILLIAMS, R. L. "A Case of Spindle-celled Sarcoma of the Sciatic Nerve associated with Von Recklinghausen's Disease," *Postgrad. Med. Journ.*, 1933, **9**, 217.

WISHART, J. H. "Case of Tumours in the Skull, Dura Mater and Brain," *Edin. Med. and Surg. Journ.*, 1822, **18**, 393.

LEGENDS FOR PLATES II AND III.

FIG. 2.—*Case* I. Cerebral cortex from the posterior part of the right middle frontal convolution. The cortex is the seat of a meningio-angiomatous condition. The subjacent white matter has the curious fenestrated appearance described in the text. (Weigert-Pal. × 2½ diam.)

FIG. 3.—*Case* I. Cerebral cortex involved in meningio-angiomatosis. A mixed meningiomatous and angioblastic condition invading the grey matter from the surface. Note the proliferation of the vessels of the leptomeninges in the sulcus and their penetration inwards along with meningiomatous cells. (Mallory's connective tissue stain. × 32.)

FIG. 4.—*Case* I. Cerebral cortex Gliomatosis in a meningio-angiomatous area. Note the proliferated glial cells; some of them are multinucleated and resemble the abnormal glial cells seen in tuberous sclerosis (the so-called "Gemastetezellen"). (Hæmatoxylin and Eosin. × 400.)

FIG. 5.—*Case* I. Transverse section through a lumbar posterior nerve root showing concentric whorls reminiscent of a meningioma; a similar tumour found upon the sciatic nerve will be seen in fig. 7. (Weigert's Hæmatoxylin and van Gieson. × 100.)

FIG. 6.—*Case* I. Lumbar cord showing extensive central gliosis with cavitation expanding and distorting cord. There is only a slight amount of demyelination. Note the small neurofibroma on a posterior nerve root. (Weigert-Pal. × 10.)

FIG. 7.—*Case* I. High power. Transverse section through sciatic nerve showing the formation of a minute concentrically arranged nodule of tumour similar to those found in many of the spinal nerve-roots. In its structure it is distinctly reminiscent of a Pacinian touch-corpuscle. (Hæmatoxylin and Eosin. × 400.)

FIG. 8.—*Case* II. Ventral aspect of the cervical and dorsal cord showing multiple tumours. The large tumour just above the cervical enlargement is seen compressing the cord.

BERGER'S α RHYTHM IN ORGANIC LESIONS OF THE BRAIN.[1]

By FREDERICK LEMERE, M.D.
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It is now generally recognized that the electrical potential changes occurring in the brain at different frequencies may be picked up from the intact scalp and recorded by means of the oscillograph. By far the most outstanding rhythm is that which has a rate of around ten waves per second (Berger's alpha waves [1]). This rhythm is present in the vast majority of cases only when the subject is at rest with his eyes shut. It seems fairly certain that the waves are produced by groups of cells beating in unison in the occipital lobe (Adrian *et al.* [2 and 3]). As soon as the subject opens his eyes and focuses on an object, the occipital cortex is no longer free to beat spontaneously and the rhythm breaks up and disappears.

The purpose of this paper will be the study of the effect of various cerebral lesions on the α rhythm. Only passing attention will be paid to the other less obvious cerebral rhythms as their nature and significance are still obscure.

MATERIAL AND METHODS.

Electroencephalograms were obtained from fifteen normal subjects and sixty patients with intracranial cerebral lesions. Each subject was examined on from three to five separate occasions at intervals of from one to seven days. A balanced input amplifier was used in conjunction with a Matthews ink-writing oscillograph.

The electrodes were gauze pads moistened with saline solution and placed against the scalp, one in front and the other at the back of the head. The rhythm from the two cerebral hemispheres was compared by taking several recordings alternately from the two sides of the head. In all the normal control records, the waves from the right side of the head were equal in height, regularity and frequency to those from the left side of the head (fig. 1).

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[1] This work was financed by a grant from the Rockefeller Foundation and carried out at the National Hospital, Queen Square, London. I wish to express my sincere gratitude to the staff of this hospital for enabling me to work there.

The diagnoses of the cases used in this investigation were made by the staff and were confirmed by autopsy, encephalography, or operation in 80 per cent. of the cases.

The instructions were for the patients to lie as quietly and as relaxed as possible and to open and shut their eyes as requested. Only those who could co-operate with this procedure were used in this investigation

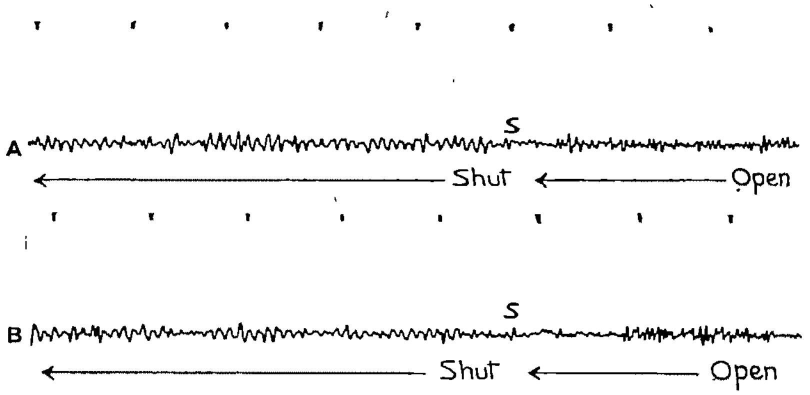

FIG. 1.—Representative sections of a record taken from a normal control subject showing the similarity of the Berger rhythm on the two sides. Time in seconds. Eyes shut at S. (A) Right side. (B) Left side.

BERGER'S *a* RHYTHM IN UNILATERAL LOCALIZED CEREBRAL LESIONS.

The following cases presented the opportunity of observing the changes in the *a* rhythm produced by the lesion on the affected side as opposed to the normal rhythm from the opposite or unaffected side. In some cases, the pathological rhythm varied from time to time, and it was considered absolutely necessary to make repeated observations before drawing any final conclusions.

Frontal lobe lesions.—Four patients were examined; one had an abscess without increased intracranial pressure, the second a tumour with increased intracranial pressure, and the third and fourth tumours without increased intracranial pressure. All but the first case showed a slightly stronger rhythm on the affected side, i.e. the waves were larger and more often present.

Parietal lobe lesions.—Three cases were examined; all were tumours, but only the third had increased intracranial pressure. The Berger rhythm again was slightly stronger on the affected side, except in the first case where the rhythm on the two sides was equal.

Deep temporal lobe lesions.—Only one case, presenting occasional uncinate fits, was observed. The *a* waves on the affected side were much stronger than on the normal side.

Parieto-temporal lobe lesions interrupting the optic radiations.—Four such cases were studied—all due to tumour. Two had increased and two had normal intracranial pressure. The *a* waves were more pronounced on the affected side and in two, where the hemianopia was complete, the rhythm was present on the affected side with the eyes open or shut. In other words, the lesion so isolated the visual cortex from the incoming visual impulses on the affected side that a spontaneous rhythm was free to develop with the eyes open or shut.

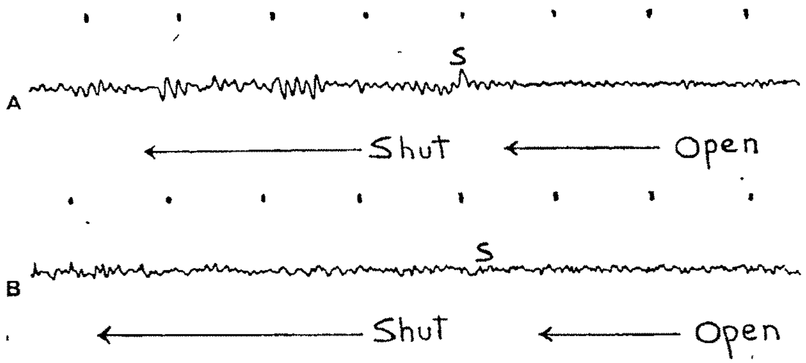

FIG. 2.—Representative sections of a record obtained in a case presenting practically complete right-sided hemianopia due to a two-year-old thrombosis of the left posterior cerebral artery. Time in seconds. Eyes shut at S. (A) Right or normal side. (B) Left or affected side with no true Berger rhythm.

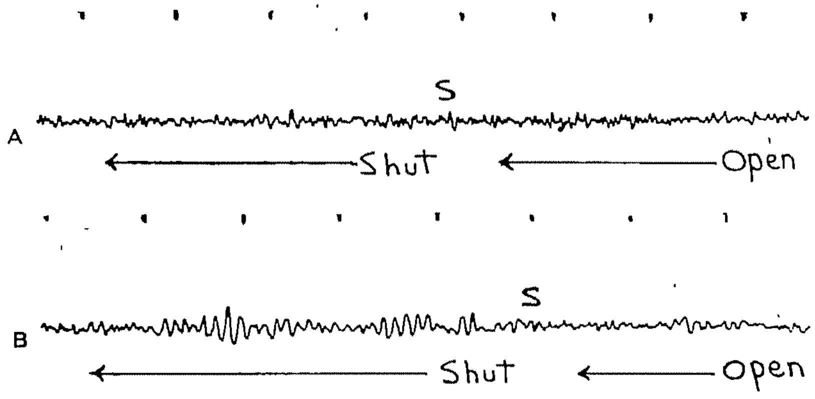

FIG. 3.—Representative sections of a record taken from a patient with a right sided basal ganglion lesion. Time in seconds. Eyes shut at S. (A) Left or normal side. (B) Right or affected side showing a markedly augmented Berger rhythm.

Occipital lobe lesions (fig. 2).—Four patients were observed: one had a cyst involving the lobe on one side, the second a tumour without associated increased pressure, and the third and fourth suffered from thrombosis of the posterior cerebral artery. The Berger rhythm was absent on the side of the lesion in the first three cases where the hemianopia was fairly complete. In the fourth case there was only a partial hemianopia and the Berger rhythm was present, but much depressed, on the affected side.

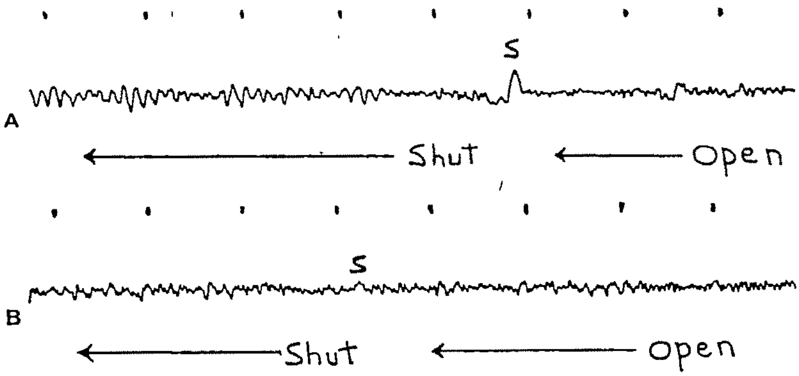

FIG. 4.—Representative sections of a record from a case presenting a thalamic syndrome on the left (lesion in the right cerebral hemisphere). Time in seconds. Eyes shut at S. (A) Left or normal side. (B) Right or affected side showing a depression of the Berger rhythm.

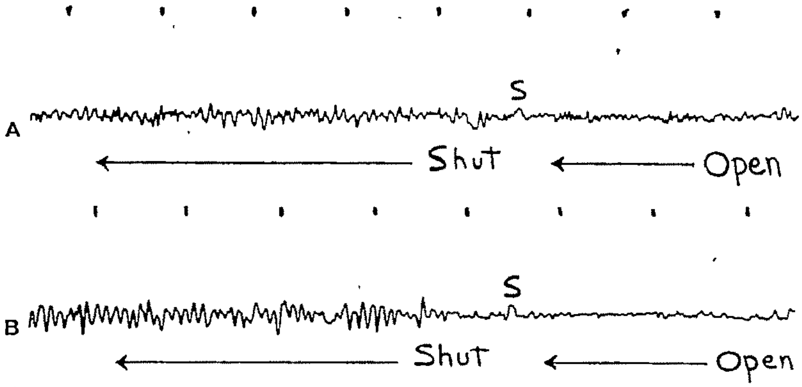

FIG. 5.—Representative sections of a record taken from a patient with a right sided fronto-parietal cortical atrophy. Time in seconds. Eyes shut at S. (A) Left or normal side. (B) Right or affected side showing an augmentation of the Berger rhythm and a depression of the beta (20 per second) waves which are most easily seen when the eyes are open.

Basal ganglion lesions (fig. 3).—Three cases presenting signs of unilateral basal ganglion lesions and loss of function were studied. In all three there was a markedly better *a* rhythm on the side of the lesion.

Thalamic lesions (fig. 4).—Five cases with a typical "thalamic" syndrome on one side were observed. The first four were apparently due to cerebral vascular lesions in the region of the thalamus and internal capsule, while the fifth was produced by a tumour in the region of the mid-brain and hypothalamus. The rhythm was depressed on the side of the lesion in all but the first case where the two sides were equal.

Cortical atrophy.—Three cases of long standing unilateral cortical atrophy were observed. The atrophy in the first case included only the frontal and parietal lobes and the *a* rhythm was increased on the affected side (fig. 5) ; in the other two, however, the atrophy included the whole hemisphere and there was an associated hemianopia. In these two cases, the *a* rhythm was very much depressed on the affected side.

Cerebellar lesions.—Two cases of tumour with mildly increased intracranial pressure were studied. No difference between the *a* rhythm from the two sides of the head was noticed.

BERGER'S *a* RHYTHM IN BILATERAL AND GENERALIZED CEREBRAL DISEASE.

Pituitary tumour (fig. 6).—Two cases of tumour without increased intracranial pressure were observed, and in both there was severe amblyopia. The *a* rhythm was equally present on both sides and was almost as strong with the eyes open as with the eyes shut.

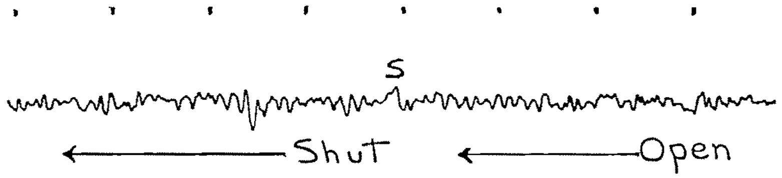

FIG. 6.—Representative section of a record taken from a patient with pituitary tumour and resulting amblyopia. Time in seconds. Eyes shut at S. Shows the Berger rhythm present with the eyes open or shut.

Bilateral lenticular disease.—Three cases of Wilson's diseases were examined. The *a* rhythm was strong in the least affected patient and less obvious in the most deteriorated one. One case of postencephalitic Parkinsonism was observed. The rhythm was apparently normal in this case.

General paresis.—Six patients were studied representing both acute, chronic, and arrested stages of the illness. In all the rhythm was rather weak.

Cerebral arteriosclerosis.—Seven cases were studied and all showed a rather poor *a* rhythm except for one patient with a history of several manic-depressive attacks [4].

Organic dementia.—Seven cases were observed, including three deteriorated epileptics, one diffuse sclerosis, one progressive muscular atrophy, one disseminated sclerosis, and one olivo-ponto-cerebellar disease. In all the *a* rhythm was rather poor.

MISCELLANEOUS OBSERVATIONS.

The normal range of Berger's *a* rhythm is between 9 and 12 beats per second [4]. In none of the cases with unilateral lesions was there a noticeable difference between the rhythm rate on the affected and on the normal side. In those cases with dementia, markedly increased intracranial pressure, and paraldehyde, morphine, or bromide intoxication, the rate was definitely on the low side, running around 7 to 8 beats per second. Berger [5] has described a slowing of the alpha waves to from 3 to 5 per second in these conditions and such waves are certainly seen. I do not believe, however, that these slow waves are modified Berger's alpha waves as they are present with the eyes open or shut.

Berger has recently stated [6] that in acute paretics the rhythm is irregular with shorter 12 to 18 per second waves interspersed amongst the regular 9 to 12 per second waves. He believes that this denotes an irritative process in the cerebral cortex and that in arrested paretics the rhythm becomes more regular. I have also noticed this irregularity in paretics, but have seen it occasionally in other conditions as well, such as mental deficiency and senility.

The nature of Berger's beta waves (those occurring at a rhythm of around 20 per second and over with the eyes open or shut) is not well understood. They seemed to be depressed the most by lesions involving the parietal lobe. In a case of complete unilateral cortical atrophy the unaffected side showed a normal rhythm, while the atrophied side showed no alpha or beta waves, but many 3 to 5 per second waves with the eyes open or shut. This suggests that the alpha and beta waves come from the cortex, while the slower 3 to 5 per second waves arise either from an organically affected cortex or subcortical centres [7].

Out of seven patients with Jacksonian fits from localized cerebral lesions, five showed sporadic spikes of relatively high voltage (fig. 7). These represented a positive potential applied to the electrode nearest the area of the lesion. There was no evidence of any convulsive phenomena at the time of these sporadic outbursts of relatively high potential. Such spikes have been described by other workers [8].

Records were obtained during migraine attacks in. two subjects. The only alteration observed was a suppression of the Berger rhythm during the visual aura, but not during the subsequent period of headache. This suggests that the mechanism of migraine is fundamentally different from that of epilepsy where there are definite electrical discharges characteristic of an attack [9].

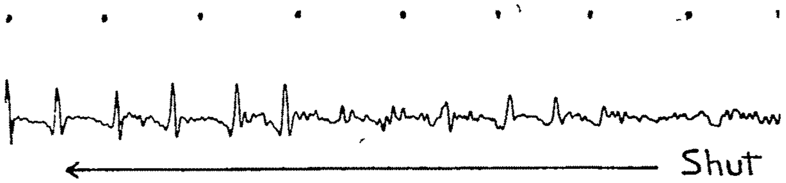

FIG. 7.—Representative section of a record from the right side of a patient with Jacksonian fits originating in the right occipital lobe. Time in seconds. Eyes shut. Represents positive potentials sporadically applied to the posteriorly placed electrode (that placed nearest the discharging focus). No signs of convulsion or visual aura.

Two cases of unilateral Horner's syndrome were observed and no difference noticed in the rhythm from the two sides. Apparently the sympathetic nerve supply to the brain has nothing to do with the activity of the cerebral cortex, at least in regard to the production of the Berger rhythm.

DISCUSSION.

It is recognized that the material presented is quite insufficient for the drawing of any final conclusions. It does, however, offer certain leads for further work and already seems to have been of some value in diagnosis. For example, in cases presenting hemianopia, and in which there is doubt as to whether the optic radiations or the occipital lobe itself is involved, a strong *a* rhythm would suggest the former while a weak or absent rhythm would favour the latter diagnosis.

In some cases a diagnosis between a frontal lobe lesion on one side or a cerebellar lesion on the opposite side presents difficulties. A difference between the two sides (especially a slightly better rhythm on the affected side) would suggest a frontal lobe lesion.

The value of potential records in the investigation of different forms of epilepsy has been discussed by Berger and recently by Gibbs and Lennox.

SUMMARY AND CONCLUSIONS.

Electroencephalograms were obtained from the two sides of the head in fifteen normal subjects and in sixty patients with intracranial lesions. In the normal subjects and in those patients with bilateral generalized cerebral lesions, Berger's α rhythm (that occurring at 10 per second with the eyes shut) was the same on the two sides.

Unilateral localized lesions of the frontal, parietal, or temporal lobes were associated in general with a slightly stronger rhythm on the affected side. Basal ganglion lesions resulted in a very much stronger α rhythm on the affected side while thalamic and hypothalamic lesions depressed the rhythm on the affected side.

Fairly complete lesions of the occipital lobe on one side resulted in a very poor or absent rhythm on that side. Lesions of the optic radiations, on the other hand, were associated with a strong α rhythm on the affected side which was even present with the eyes open, provided the hemianopia was fairly complete.

The suggestion of Adrian and Matthews that the α rhythm is produced in the cortex of the occipital lobe seems to offer the best basis for the interpretation of the effect of these unilateral lesions. Any lesion tending to isolate, but not involve, the occipital lobe caused a strengthening of the rhythm on the affected side. Any lesion involving the greater part of the occipital lobe, on the other hand, produced an almost complete absence of rhythm on the affected side. The depressing effect of thalamic lesions on the α rhythm on the affected side is less easily understood and requires further investigation.

REFERENCES.

[1] Berger, Hans. "Das Elektrenkephalogramm des Menschen," *Die Naturwissenschaften*, 1935, **23**, 121.

[2] Adrian, E. D., and Matthews, B. H. C. "The Berger Rhythm: Potential Changes from the Occipital Lobes in Man," *Brain*, 1934, **57**, 355.

[3] Adrian, E. D., and Yamagiwa, K. "The Origin of the Berger Rhythm," *ibid.*, 1935, **58**, 323.

[4] In an article in *Brain*, 1936, **59**, 366, I have pointed out that manic-depressive patients have a much stronger Berger rhythm than schizophrenic patients.

[5] Berger, Hans. "Ueber das Elektrenkephalogramm des Menschen," *Arch. f. Psychiat.*, 1932, **97**, 6.

[6] *Idem.* "Ueber das Elektrenkephalogramm des Menschen," *ibid.*, 1936, **104**, 678.

[7] With the method used in this investigation these slow waves were not seen in normal people. They have been described, however, by several authors as occurring during normal sleep.

[8] Jasper, H. H., and Andrews, H. L. "Human, Brain Rhythms: I, Recording Techniques and Preliminary Results," *Journ. Gen. Psychol.*, 1936, **14**, 98.

[9] Gibbs, F. A., Davis, H., and Lennox, W. G. "The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness," *Arch. Neurol. and Psychiat.*, 1935, **34**, 1133.

THE CORTICAL PROJECTION OF THE PULVINAR IN THE MACAQUE MONKEY.

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THE view is generally held that the pulvinar, which forms the posterior pole of the thalamus, projects on to that part of the parietal lobe which lies closely adjacent to the visual cortex. In 1933 and 1934 (Clark and Boggon, 1935) a series of experiments were carried out with the object of defining the thalamo-cortical connections in the macaque brain by the study of cellular atrophy in the thalamus following localized cortical lesions. It was found that, with lesions placed in different parts of the parietal lobe, very little secondary atrophy in the pulvinar ensued. It was assumed that, unless its projection on to the cortex is distributed very diffusely, the main element of the projecting pole of the pulvinar has little, if any, direct connection with the parietal cortex. On the other hand, evidence was brought forward which indicated that the intergeniculate nucleus of the pulvinar (element *pd* of Friedemann) projects on to the periparastriate areas of the cortex—that is to say, Brodmann's areas 18 and 19. These results were held to be consistent with Poliak's conclusion (1932), based on Marchi studies, that very few fibres from the pulvinar reach the cortex. However, in 1935, there appeared a report by Earl Walker of the cell degeneration in the thalamus following complete hemi-decortication in two monkeys. In one case all the cells of the pulvinar had undergone complete atrophy, while in the other the pulvinar had "practically completely degenerated." These results must be taken to indicate that at least the greater part of the pulvinar does in fact project on to the cerebral cortex. Since most of the parietal cortex has been excluded on the basis of cell degeneration experiments as the destination of these projection fibres (except those arising from element *pd*), it remains to be determined what are the cortical connections of the main element of the pulvinar. A clue was provided to this problem in the course of some experiments recently undertaken for the study of the thalamic connections of the temporal lobe (Clark, 1936). It was found that lesions involving the middle part of the superior temporal gyrus and the lips of the Sylvian sulcus were followed not only by retrograde cell degeneration in the medial geniculate body, but also by a well-defined patch of atrophy in the main element ($p\beta$) of the pulvinar. It was concluded, on the basis of these observations, that "the pulvinar projects, in part at least, on to the posterior Sylvian receptive region of the cortex"—a region which Poliak (1932) first described as extending back from the auditory area along the walls and lips of the Sylvian sulcus as far as its caudal extremity.

The present experiments have been designed with the purpose of clearing up the doubtful points which remain in regard to the cortical projection of the pulvinar. In the first experiment the whole of the parietal lobe on the lateral surface of the cerebral hemisphere was removed in order to define the maximum relation between the cortex of this lobe and the pulvinar. In the second case the cortical ablation was limited to the whole extent of the posterior Sylvian receptive area. Lastly, in two monkeys portions of areas 18 and 19 were removed in order to test the suggestion previously made that this part of the cortex receives fibres from the intergeniculate nucleus of the pulvinar.

METHODS.

As in previous experiments of the same kind, the operations were performed under nembutal anæsthesia. The cerebral hemisphere was exposed by raising an osteoplastic flap, and the cortical lesion was made with the aid of an endothermy apparatus. The animals were kept for approximately six weeks, after which they were sacrificed by an overdose of chloroform. On removal of the brain the lesion was measured and its appearance reproduced to scale in a free-hand drawing. The cortical lesion and the corresponding half of the thalamus were sectioned and stained with Borell's methylene blue. Representative sections of the thalamus were traced by means of a projection apparatus, with the delineation of the various nuclear elements and the area of cell atrophy. In all cases the area of atrophy was well defined and quite sharply circumscribed. A photomicrograph of one of these degenerated areas (from Experiment A) is shown in Plate IV, fig. 1, to indicate the degree of their definition. The nomenclature of the nuclear elements of the pulvinar used here is that employed by Friedemann in his photomicrographic atlas of the cercopitheque thalamus published in 1911-12.

EXPERIMENTAL RESULTS.

Experiment A.—O.M. 113. Operated December 19, 1935, killed February 19, 1936.

In this case an extensive ablation of the parietal lobe of the left cerebral hemisphere was made. The animal made a very rapid recovery from the operation. For a few days it showed a marked weakness of the right arm and leg, but within a week of the operation this paresis had disappeared and the animal's movements appeared quite normal.

Immediately after death the brain was removed and the extent of the lesion reproduced as accurately as possible in a diagram (fig. 1A). Superficial examination showed that it had involved almost the entire parietal lobe except for a narrow strip of cortex along the caudal lip of the central sulcus. Above, the lesion just reaches the upper margin of the hemisphere. Behind it involves the anterior lip of the occipital operculum in its dorsal half. The lower extremity of the superior lunate sulcus can be seen emerging from the postero-inferior angle of the lesion. The lower border of the lesion lies on a level with the inferior extremity of the central sulcus, and it extends forwards involving the upper buried surface of the superior temporal gyrus as far as the posterior end of the insula. The rostral border of the lesion reaches to within 2 mm. of the central sulcus at its upper end, and 7 mm. at its lower end. The whole lesion measures 23 mm. in its antero-posterior extent and 30 mm. in vertical diameter.

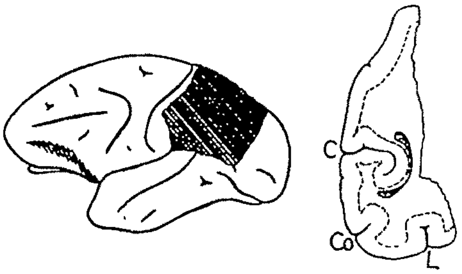


FIG. 1A. FIG. 1B.

FIG. 1A.—The cortical lesion in Experiment A. × ½.
FIG. 1B.—Coronal section through the middle of the lesion in Experiment A. × 1.
C.—Calcarine sulcus. *Co.*—Collateral sulcus. *L.*—Lower end of lunate sulcus.

Figure 1B shows a drawing of a vertical section through the middle of the lesion. It will be noted that the lesion extends deeply into the white matter, encroaching on the dorsal half of the optic

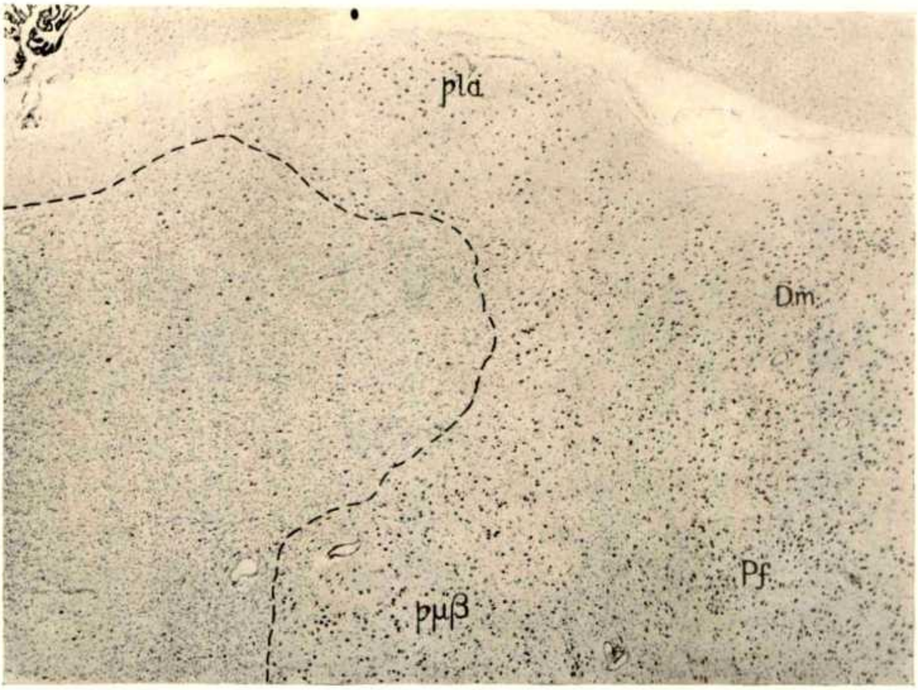


FIG. 1.—Transverse section through the pulvinar in Experiment A, showing the area of cell atrophy to the left. × 28.

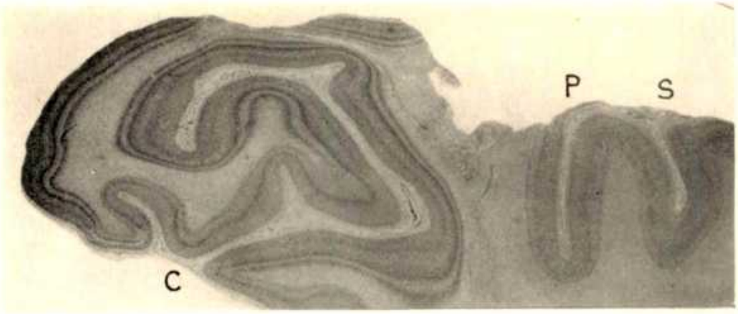


FIG. 2.—Antero-posterior section through the middle of the lesion in Experiment C. *C*. Calcarine sulcus. *P*. Parallel sulcus. *S*. Sylvian sulcus.

To illustrate paper by W. E. Le Gros Clark and D. W. C. Northfield.

radiations close to the lateral aspect of the posterior horn of the lateral ventricle. It also involved the peristriate areas and the rostral border of the area striata, and also almost all the area post-centralis except that part which lies buried in the posterior wall of the sulcus.

The thalamus.—Serial sections through the length of the thalamus show considerable areas of complete cell atrophy accompanied by a dense gliosis. For descriptive purposes these sections may be traced in a rostral direction. The first section of the first block passes through the extreme tip of the projecting pole of the pulvinar. In section 120 a small patch of cell atrophy and gliosis appears at the dorso-lateral angle of the pulvinar where it comes into continuity with the internal capsule. Sixteen sections later, the first block comes to an end. Here the patch of complete cell degeneration is very distinct, and from it a zone of gliosis and partial cell atrophy extends for some little distance into the centre of the pulvinar and medially along its dorsal surface, involving Friedemann's elements *pβ* and *pμ* (fig. 2*b*).

The first section of the second block cuts through the middle of the medial geniculate body, the base of the main element of the pulvinar *pβ*, the intergeniculate nucleus, the posterior commissure, and the habenular ganglion. At this level most of the pulvinar had undergone complete secondary degeneration. The portions which are left intact comprise a strip along the medial border of element *pβ*, the most ventral part of *pμ*, the whole of *pa*, and the intergeniculate nucleus (fig. 2*c*). There is also a thin row of normal cells along the dorsal surface of the pulvinar. A corresponding extent of the nucleus reticularis has also undergone atrophy. The medial geniculate body at this transverse level is quite normal, and no definite signs of cell degeneration or gliosis could be detected in the pretectal nucleus. It is to be noted that there is a very sharp line of demarcation between the atrophic zone and the normal elements. A few sections further forwards, the atrophic area extends ventrally into the upper border of the intergeniculate nucleus, *pd*. At Section 60, the posterior ends of the parafascicular and dorsomedial nuclei and the caudal extremity of the lateral half of the lateral geniculate body appear. All these elements are normal here. Practically complete cell degeneration involves the caudal ends of the lateral nucleus and the pars externa of the ventral nucleus. A group of normal cells lies close against the medial medullary lamina, representing a portion of element *pμβ* of the pulvinar. Element *pla* is also intact. More ventrally the dorsal part of the intergeniculate nucleus is seen to be entirely atrophied. There is also a considerable degree of secondary

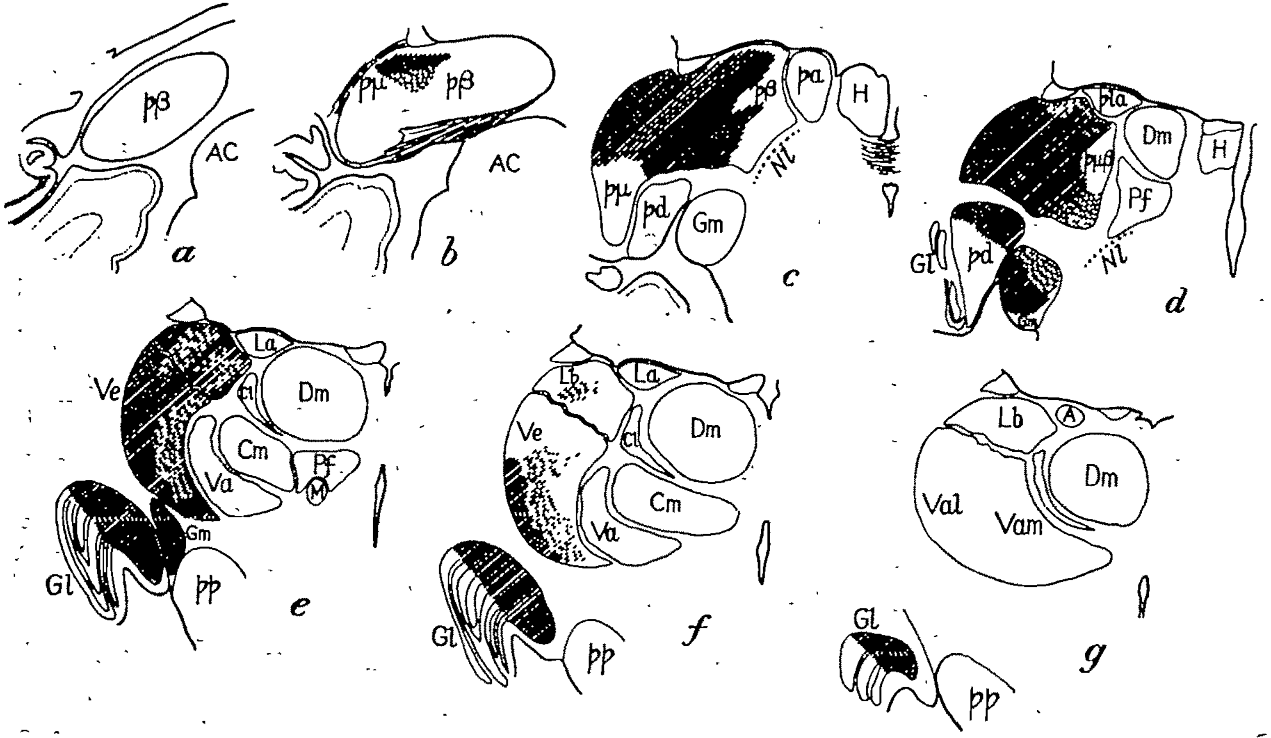


FIG. 2.—Transverse sections through the thalamus in Experiment A. In this and similar diagrams the areas of complete cell atrophy are indicated by hatching, while areas in which cell degeneration is partial are marked by interrupted lines.

degeneration affecting the medial geniculate body in most of its extent at this level, except at its medio-ventral angle. However, there are numerous scattered normal cells in the atrophied part of this nucleus (fig. 2*d*). A few sections more rostrally the whole of the medial geniculate body becomes almost completely atrophied except for a small group of cells at its ventral border. Here the whole transverse extent of the lateral geniculate body comes into view. The whole of its medial half is completely atrophied, a sharp line down the median axis of the nucleus separating the normal from the degenerated part. The degeneration of the medial half of the lateral geniculate body extends throughout its antero-posterior length.

At section 110, which cuts through the rostral pole of the medial geniculate body, the pars externa and the pars arcuata of the ventral nucleus become defined. The whole of the pars externa has at this level undergone complete cell atrophy except for scattered normal cells in its medial part. Similarly, almost all the cells of the nucleus lateralis *b* have disappeared except for a group of scattered cells in its central and dorsal part. Element *La* of the lateral nucleus remains intact and the cyto-architecture of the pars arcuata of the ventral nucleus also appears normal. There is no evidence of any secondary degeneration or gliosis in the dorso-medial, centre median, parafascicular or lateral central nuclei. The rostral pole of the medial geniculate body is completely atrophied (fig. 2*e*). A few sections further forwards (section 125) the normal cells at the medial border of the pars externa of the ventral nucleus form a much more conspicuous group, though their density is still less than normal. Normal cells also become more numerous in element *Lb*, especially at its dorso-lateral angle (nucleus angularis of Friedemann). At section 160 very little complete atrophy remains except for the medial half of the lateral geniculate body (fig. 2*f*). There is still considerable gliosis throughout the greater part of the pars externa of the ventral nucleus, and a zone of almost complete cell atrophy persists along its ventro-lateral margin. Further, in the middle of this element there is a partial atrophy. In nucleus *Lb* a slight degree of partial atrophy only is to be observed in its centre.

The first section of the third block cuts through the rostral pole of the lateral geniculate body, the medial half of which still shows complete degeneration. All the other elements of the thalamus at this level and further forwards are entirely normal in their cyto-architecture (fig. 2*g*).

In summarizing the results of this experiment, it may first be noted that the complete degeneration of the medial half of the lateral geniculate body is evidently due to the extension of the lesion into the dorsal half of the area striata of the cortex and to its encroachment on the dorsal half of the optic radiations close to the lateral wall of the posterior horn of the lateral ventricle. The atrophy in the rostral part of the medial geniculate body is the result of the involvement of the caudal part of the auditory area within the lips of the Sylvian fissure, as well as of a portion of the auditory radiations. Almost the whole of that part of the pars externa of the ventral nucleus which receives the termination of the fillet system has undergone secondary degeneration, associated with the destruction by the lesion of the post-central gyrus. However, a zone of normal cells persists along the medial aspect of this thalamic element, and it is probable that this is due to the fact that the lesion did not extend so close to the central fissure at its lower end, leaving here a considerable part of the face area of the general sensory cortex. It is a noteworthy fact that the pars arcuata of the ventral nucleus seems to have escaped atrophy. Previous observations have shown that this element of the ventral nucleus projects on to the precental gyrus (Clark, 1936). The degeneration in the posterior part of nucleus *Lb* is probably related to the destruction of areas 5 or 7, or both, in the post-sensory parietal cortex (*see* Clark and Boggon, 1935).

The cell atrophy in the pulvinar must evidently be due to the involvement by the lesion of some other part of the parietal lobe, or the posterior end of the temporal lobe.

Experiment B.—O.M. 55. Operated March 27, 1936, killed May 6, 1936.

This experiment consisted in a local ablation of the posterior Sylvian receptive region defined by Poliak on the basis of Marchi studies. This region extends along the walls of the Sylvian sulcus from the auditory area to its posterior extremity. The extent of the lesion is shown in figs. 3 and 4. Rostrally it reaches to the level of the lower end of the central sulcus, 14 mm. behind the Sylvian point. Above it extends as far as the middle part of the intraparietal sulcus. Below and behind it involves the exposed surface of the superior temporal gyrus, the main lesion being limited by the upper lip of the parallel sulcus. The lesion is 12 mm. wide near its rostral extremity and 8·5 mm. wide near its posterior extremity. It is 26 mm. in length. The illustration shows that anteriorly it involves the lower end of the post-central gyrus (areas 1, 2 and 3). Transverse sections were taken through the length of the lesion. From these it is clear that the cortical injury was almost entirely confined to the immediate boundaries of the Sylvian sulcus. However, there are two superficial abrasions of the exposed cortex below the caudal half of the parallel sulcus (in Areas 18 and 19) as well as two very small abrasions on the surface of the area striata behind the lunate sulcus (fig. 1). In addition, there is a slight involvement of the insular cortex in the Sylvian fossa.

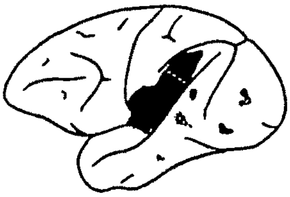


FIG. 3.—The cortical lesion in Experiment B. × ½.

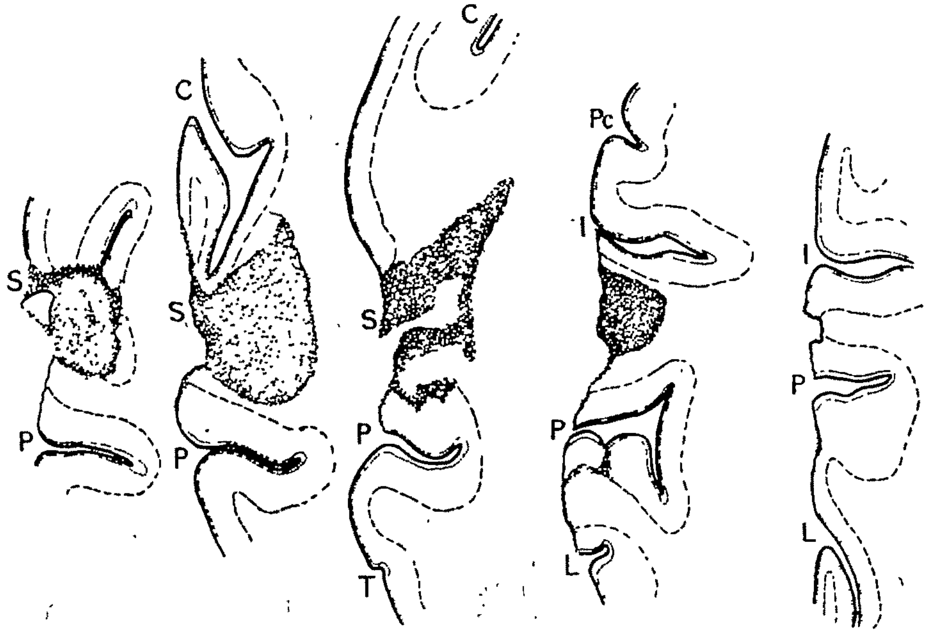


FIG. 4.—Transverse sections taken at regular intervals antero posteriorly through the lesion in Experiment B. *C.*—Central sulcus. *I.*—Intraparietal sulcus. *L.*—Lunate sulcus. *P.*—Parallel sulcus. *Pc.*—Post-central sulcus. *S.*—Sylvian sulcus.

The thalamus.—Serial sections through the thalamus show considerable cell atrophy in its caudal part. The first sections of the first block cut through the tip of the pulvinar. Here the cyto-architecture of the pulvinar (element $p\beta$) is normal. Further forward, where the pulvinar becomes adherent to the side of the mid-brain, a patch of partial cell

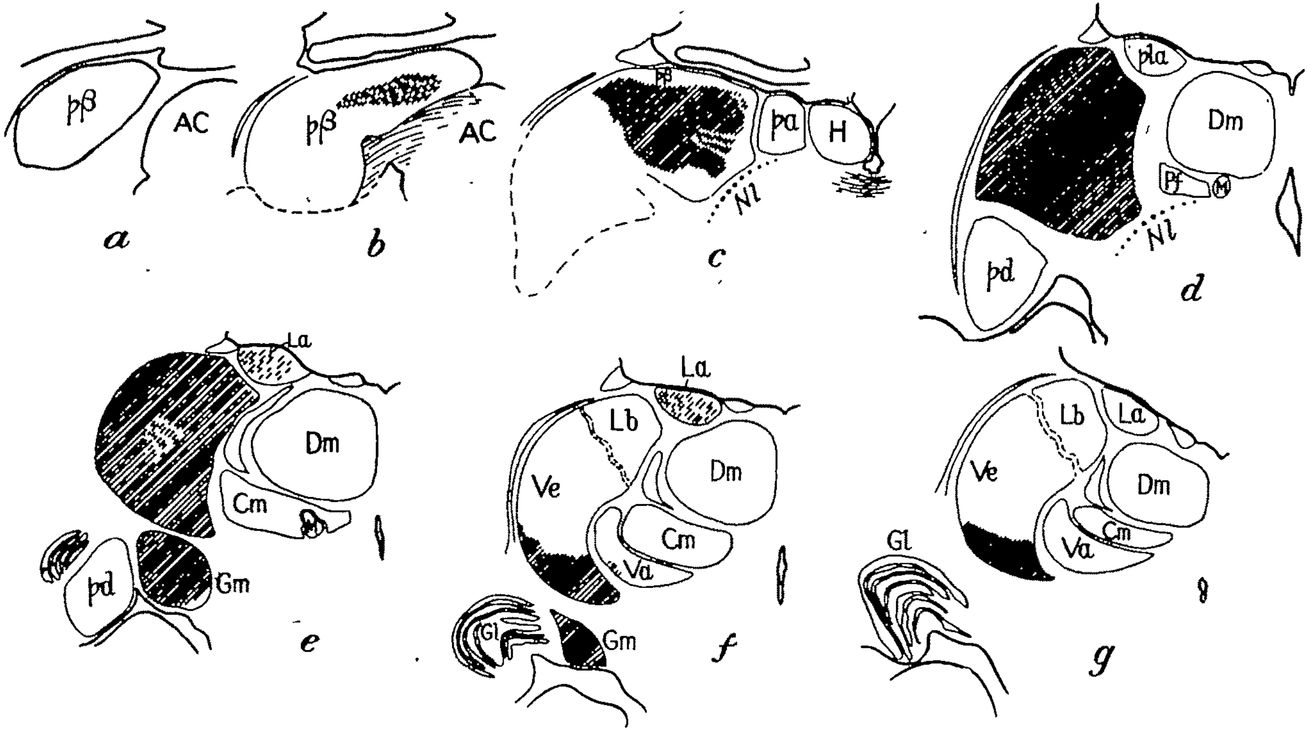


Fig. 5.—Transverse sections through the thalamus in Experiment B showing the areas of cell degeneration.

atrophy appears in its dorso-medial part extending laterally towards the centre (fig. 5*b*). In this area there is a conspicuous thinning out of the cells with an accompanying gliosis. For a number of sections this area of secondary degeneration remains fairly constant. By section 176, however, it has become quite large and extremely well defined. Here it extends over almost the whole of the dorsal half of the pulvinar involving the element *pβ*. There remains a zone of normal cells at the dorsal surface, and element *pa* (at the side of the habenular nucleus) is quite unaffected. Ventral to the cortico-tectal fasciculi (which penetrate the pulvinar at this level) there is no sign of cell atrophy. In other words elements *pd* and *pη* appear normal. Thus the area of atrophy is confined to element *pβ*, and it is interesting to note the sharp contrast between this degenerated element and the other normal elements of the pulvinar. This area of atrophy preserves relatively the same extent to the end of the first block, which cuts through the habenular ganglion and the posterior commissure.

The first section of the second block cuts through the rostral part of the pulvinar and the caudal end of the dorso-medial nucleus (fig. 5*d*). At this level the pulvinar is completely atrophied except for elements *pd* and *pla*. The latter are entirely normal in their cyto-architecture. At section 42 the caudal ends of the geniculate bodies appear. The medial geniculate body is entirely atrophied throughout its antero-posterior extent except for a small group of normal cells at its ventro-medial angle. The lateral geniculate body shows a thin band of cell atrophy in its caudal third occupying the ventro-lateral segments of its laminæ. This slight degeneration is evidently the result of the small abrasion of the visual cortex already referred to. By section 80, odd normal cells begin to appear in the dorsal part of the atrophic area. Towards the rostral pole of the medial geniculate body, the elements of the ventral nucleus of the thalamus become evident (fig. 5*f*). Here cell degeneration is mainly confined to the ventral third approximately of the pars externa of the ventral nucleus, and the medial geniculate body. There is also quite distinct partial cell degeneration in element *La* of the lateral nucleus, especially in its ventral half. The pars arcuata of the ventral nucleus is entirely normal except only for a suggestion of partial atrophy in a small zone at the middle of its lateral border. The centre median and dorso-medial nuclei and the nucleus of the medial medullary lamina (nucleus centralis lateralis) are intact. As the sections are traced further forwards the area of cell atrophy in the pars externa of the ventral nucleus shrinks down to its ventro-medial angle.

The third block cuts through the middle of the lateral geniculate body and the rostral part of the centre median nucleus. Here the zone of cell atrophy is confined to the ventro-medial angle of the pars externa of the ventral nucleus. The pars arcuata and the centre median nucleus are normal, and, at this level, element *La* of the lateral nucleus also shows no cell degeneration. Rostral to the level of the centre median and arcuate nuclei, no more cell atrophy is evident.

Experiment C.—O.M. 157. Operated September 14, 1936, killed October 26, 1936.

This experiment involved the removal of the dorsal half of cortical areas 18 and 19 on the exposed surface of the brain. After death the lesion was found to measure 24 mm. in vertical diameter, reaching to within 6 mm. of the dorsal margin of the hemisphere above, and below almost to the extremity of the superior lunate sulcus. Rostrally it extends to the caudal lip of the parallel sulcus, and caudally it involves the opercular lip of the striate area. In addition there was found to be a small superficial abrasion of the striate area near the upper half of the occipital pole (fig. 6 and Plate IV, fig. 2).

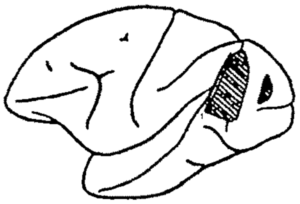


FIG. 6.—The cortical lesion in Experiment C. × ½

The thalamus.—Sections through the extreme pole of the pulvinar show a perfectly normal cyto-architecture. As the sections are traced forwards a small patch of gliosis and partial cell atrophy appears at the lateral margin of the pulvinar, involving here element *pη* of Friedemann (fig. 7*a*). This small area of degeneration remains relatively of the same size through a number of sections and is quite sharply localized. At the level at which the pulvinar becomes adherent to the side of the mid-brain (fig. 7*b*), the atrophic area is slightly more expanded, forming here a wedge-shaped patch extending into the ventral part of the pulvinar from its lateral margin. The main part of the pulvinar—element *pβ*, and other elements such as *pa* and *pla* are unaffected. Further rostrally, where the cortico-tectal fasciculi come into view cutting off element *pd* below from the rest of the pulvinar, the affected cells form a sharply circumscribed area of total cell atrophy in the dorso-lateral quadrant of *pd* (fig. 7*c*). The caudal extremity of the lateral geniculate body shows a complete degeneration of its dorso-medial half, all layers being involved. At this level (fig. 7*d*) the atrophic area in the pulvinar is confined to a tiny patch in the dorsal angle of element *pd*. A few sections further forwards this area of degeneration has disappeared. At its maximum size in transverse section, the area of atrophy in the pulvinar measures 2·8 by 1·7 mm., while its antero-posterior diameter (extending over 120 sections) is estimated at 1·8 mm. In relation to the extent of the cortical lesion, the cell atrophy in the pulvinar is therefore quite restricted.

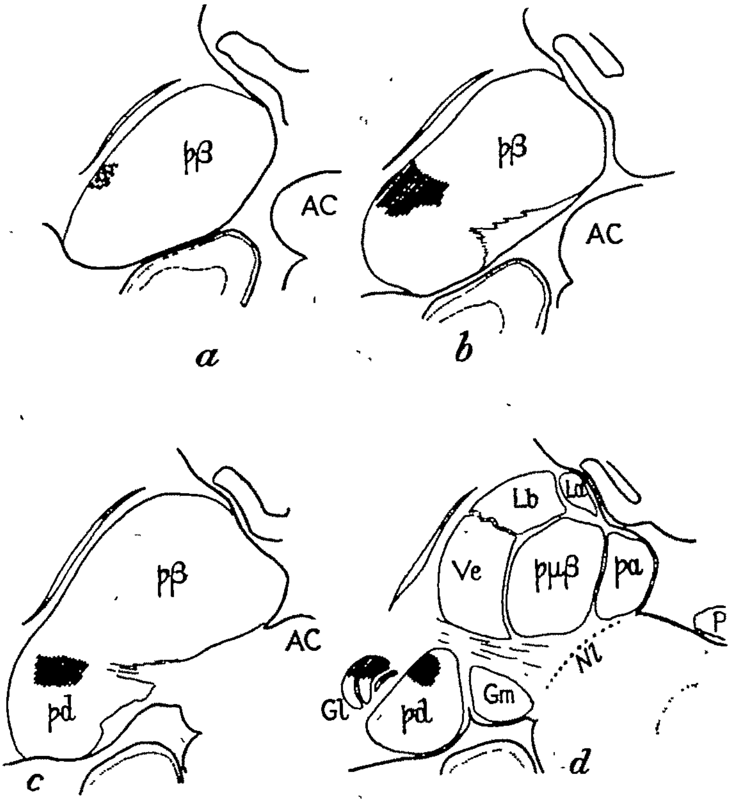
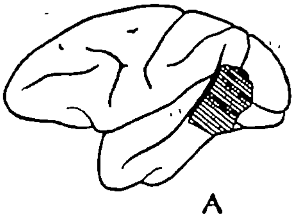


FIG. 7.—Transverse sections through the pulvinar in Experiment C, showing the areas of cell atrophy.

Experiment D.—O.M. 158. Operated September 15, 1936, killed October 27, 1936.

In this animal, the lower half of areas 18 and 19 on the exposed surface of the cerebral hemisphere was excised. The extent of the lesion as seen after death is shown in fig. 8. It was found to measure



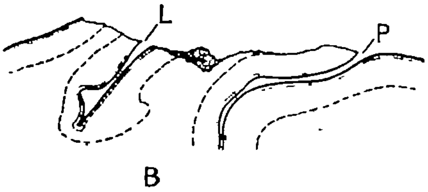


FIG. 8A.—The cortical lesion in Experiment D. × ½.

FIG. 8B.—Antero-posterior section through the middle of the lesion in Experiment D. × 2½. *L.*—Lunate Sulcus. *P.*—Parallel sulcus.

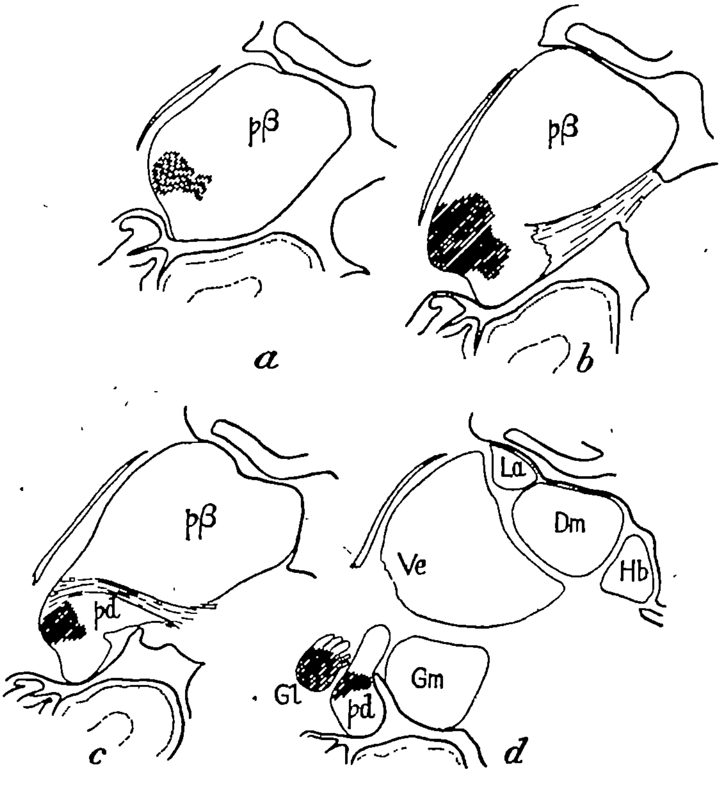


FIG. 9.—Transverse sections through the pulvinar in Experiment D, showing the areas of cell atrophy.

23 mm. in vertical and 17 mm. in antero-posterior diameter. Rostrally it reaches to the caudal lip of the parallel sulcus, and behind involves the opercular lip of the striate area. Above it extends to the upper end

of the Sylvian sulcus, 17 mm. from the dorsal margin of the hemisphere, and below to the lower margin of the hemisphere.

The thalamus.—The cyto-architecture at the extreme pole of the pulvinar is normal. Seventy sections in front of the tip of the pole, a small patch of gliosis and partial cell atrophy appears at the ventro-lateral angle of the pulvinar. This becomes more distinct a few sections further forwards, and extends somewhat medially (fig. 9*a*), and it soon forms a well-defined patch of almost complete cell atrophy confined to Friedemann's element *pη*. Where the cortico-tectal fasciculi come into view, the area of gliosis and cell atrophy is limited to that part of the pulvinar lying ventrally, i.e. in the lateral half of element *pd*. Beyond this level, the area diminishes in size, though remaining sharply circumscribed (fig. 9*c*). Further rostrally, the lateral geniculate body appears, showing complete atrophy of the cells in its ventro-lateral half. Here the degeneration in element *pd* is limited to a tiny patch near its centre, which disappears in a few sections. At its maximum development in cross-sectional area, the patch of cell atrophy in the pulvinar measures 2 8 mm. by 2·4 mm. Its antero-posterior extent, as estimated from the number of sections, is approximately 3·4 mm.

DISCUSSION.

In Experiment A, the ablation of the whole of the exposed area of the parietal lobe of the cortex (including Poliak's posterior Sylvian receptive area) was followed by extensive cell atrophy in the main nuclear element of the pulvinar (*pβ*) except at its caudal pole, and in the dorsal half of the intergeniculate nucleus (element *pd*). Previous experiments (Clark and Boggon, 1935) have suggested that element *pd* projects on to the periparastriate areas (Brodmann's areas 18 and 19), while isolated lesions in the parietal cortex (not involving the posterior Sylvian receptive region) were not followed by atrophy in the main element, *pβ*, of the pulvinar. The results of Experiment A may therefore be taken to indicate that element *pβ* projects on to the posterior Sylvian receptive area. The second experiment of the present series was devised in order to test this conclusion. In this case, a cortical lesion limited to the Sylvian area was followed by cell atrophy in the main element of the pulvinar almost identical in its extent with that in Experiment A, while the intergeniculate nucleus remained intact. Thus it appears certain that the main element of the pulvinar projects on to the cortex forming the walls and lips of the Sylvian sulcus. Previous experiments have indicated that this cortex extends forwards to become contiguous with the audito-sensory area of the superior temporal gyrus (Clark, 1936), for in two cases in which a relatively small lesion was made in this gyrus, cell atrophy in the medial geniculate body was accompanied by an area of degeneration in the main element of the pulvinar, *pβ*. In order to test the inference from Experiments A and B that the periparastriate areas receive fibres from element *pd* of the pulvinar, Experiments C and D were performed in which lesions were confined to the upper and lower halves approximately of these areas on the lateral surface of the hemisphere. In both these cases a well-marked area of cell atrophy was found in element *pd* of the pulvinar and in its caudal extension, element *pη*. Moreover, it appears that the upper and lower parts of these areas are related to the dorsal and ventral parts of *pd* respectively. On the other hand the main element of the pulvinar was unaffected. Thus it may be regarded as certain that areas 18 and 19 on the lateral surface of the brain receive fibres only from quite a limited portion of the pulvinar, i.e. elements *pd* and *pη*. It is extremely probable that this is also the case with the equivalent cortical areas on the medial surface of the brain. Walker (1936) has recently reported an experiment (Case 9, MY) in which a lesion was made involving most of area 18 and a considerable portion of area 19 on the lateral surface of a monkey's brain, and from his description it seems also that these areas on the medial surface were almost totally destroyed. The retrograde cell degeneration was more extensive than in either Experiment C or D of this paper, but it was apparently confined to elements *pd* and *pη* of the pulvinar. In spite of this, Walker, in his general summary, suggests that the whole of the pulvinar projects on to areas 18 and 19. That this is not the case is rendered certain by the present observations. In a paper dealing with the cerebral representation of the retina in the chimpanzee, Poliak and Hayashi (1936) note that, following a lesion involving areas 18 and 19 of the cortex in this animal, there was marked partial degeneration in the pulvinar, but they do not state its localization. In an experiment reported elsewhere (Clark, 1936), a lesion involving the rostral extension of areas 18 and 19 on the lateral aspect of the hemisphere led to no secondary degeneration in the thalamus. The sections of the thalamus of this case (O.M. 87) have since been re-examined, confirming the observation that the cyto-architecture of the pulvinar appears to be quite unaffected. Thus it seems probable that element *pd* projects, at least mainly, on to that region of the cortex which is immediately adjacent to the striate area—possibly to area 18 only. It may be inferred, further, that the two cortical areas which receive fibres from the pulvinar are separated by a zone of cortex which is not related to the thalamus by ascending connections. It may be noted that in these experiments no cell degeneration was present in the extreme caudal pole of the pulvinar, or in the well-defined element *pa* (which lies alongside the habenular nucleus).

The conclusion that two separate portions of the pulvinar are related by thalamo-cortical fibres to two different areas of the cortex raises the question of the nature of the impulses which they are concerned with transmitting. This must remain unsettled until something is known of the ascending connections of the pulvinar from lower levels. Internuclear connections between the pulvinar and the lateral geniculate body have been described by several authors on the basis of normal Weigert preparations, but the uncertainty of this type of evidence allows of no positive conclusions. The fact that the cells of the lateral geniculate body all degenerate after destruction of the striate cortex suggests that in fact this body is entirely concerned with cortical projection. Brouwer (1923) has shown on the basis of Marchi studies (and his work has since been confirmed) that optic tract fibres almost certainly do not terminate in the pulvinar, and a recent study of the termination of ascending tracts from the spinal cord and brain-stem (Clark, 1936) failed to show that any fibres from these sources reach it.

CONCLUSIONS.

Experimental study of secondary degeneration following cortical lesions indicates that the pulvinar, in regard to its cortical projection, can be divided into two parts. The line of separation between them is marked out approximately by the bundle of cortico-tectal fibres which penetrates the pulvinar to reach the mid-brain. Element *pd* (with its caudo-lateral extension $p\eta$), which lies in close topographical relation to the lateral geniculate body, projects on to that part of the peri-parastriate area which lies immediately adjacent to the visual cortex. The main element of the pulvinar, $p\beta$, projects on to the posterior Sylvian receptive region which was originally defined by Poliak on the basis of Marchi studies. This region extends forwards along the Sylvian fissure to become contiguous with the auditory projection area of the medial geniculate body in the superior temporal gyrus.

The cost of the animals used in this research was met by a grant from the Royal Society, which we wish gratefully to acknowledge.

ABBREVIATIONS.

A.	Anterior nucleus.
AC.	Anterior colliculus.
Cl.	Nucleus centralis lateralis.
Cm.	Centre median nucleus
Dm.	Dorso-medial nucleus.
Gl.	Lateral geniculate body.
Gm.	Medial geniculate body.
H.	Habenular nucleus.
La.	Elements of the lateral nucleus.
Lb.	
M.	Meynert's bundle.
Nl.	Nucleus limitans.
Pf.	Parafascicular nucleus.
pa.	Nuclear elements of the pulvinar.
pβ.	
pd.	
pla.	
pμ.	
pμβ.	
pp.	Pes pedunculi.
Va.	Pars arcuata of the ventral nucleus.
Val.	Pars antero-lateralis of the ventral nucleus.
Vam.	Pars antero-medialis of the ventral nucleus.
Ve.	Pars externa of the ventral nucleus.

REFERENCES.

Brouwer, B. "Experimentell-anatomische Untersuchungen über die Projektion der Retina auf die primären Opticuszentren," *Schweiz. Arch. f. Neurol. und Psych.*, 1923, **13**, 118.

Clark, W. E. Le Gros. "The Thalamic Connections of the Temporal Lobe of the Brain in the Monkey," *Journ. Anat.*, 1936, **70**, 447.

Idem. "The Termination of Ascending Tracts in the Thalamus of the Macaque Monkey," *ibid.*, 1936, **71**, 7.

Clark, W. E. Le Gros and Boggon, R. H. "The Thalamic Connections of the Parietal and Frontal Lobes of the Brain in the Monkey," *Phil. Trans. Roy. Soc.*, Series B, 1935, **224**, 313.

Friedemann, M. "Die Cytoarchitektonic des Zwischenhirns der Cercopitheken," *Journ. f. Psych. u. Neur.*, 1912, **18**, 308.

Poliak, S. "The Main Afferent Fibre Systems of the Cerebral Cortex in Primates," Univ. of California Publ. in *Anat.*, 1932, **2**, 1.

Poliak, S., and Hayashi, R. "The Cerebral Representation of the Retina in the Chimpanzee," *Brain*, 1936, **59**, 51.

Walker, A. E. "The Retrograde Cell Degeneration in the Thalamus of Macacus Rhesus Following Hemidecortication," *Journ. Comp. Neur.*, 1935, **62**, 407.

Idem. "An Experimental Study of the Thalamo-Cortical Projection of the Macaque Monkey," *ibid.*, 1936, **64**, 1.

NOTICES OF RECENT PUBLICATIONS.

Handbuch der Neurologie, Herausgegeben von O. BUMKE und O. FOERSTER. Berlin: Julius Springer.

The latest volumes of this System of Neurology to appear attain the same high standard as their predecessors and confirm the earlier impression that the whole system is essential to the neurologist who would keep up to date in his profession. The comprehensive bibliographies at the end of every chapter are a particularly valuable supplement to the full and authoritative treatment of each subject.

Band VI. *Grosshirn, Vegetatives Nervensystem, Körperbau und Konstitution.* S. 1153, mit 549 Abbildungen. Price RM. 223.

This valuable and excellent volume presents an extremely interesting study of the functions and pathology of the brain, for the two last sections, on the vegetative system and constitution, occupy only a relatively small part of it. In the first 450 pages Foerster deals with the cerebral systems of motion and sensation. In each of these chapters he first describes the anatomical structures which underlie these functions, and then deals with the results of their electrical stimulation in the human brain, a subject in which his experiences are unrivalled. It is already known that the "motor areas" of the cortex which he defines are much more extensive than they are generally accepted to be; any area from which he has been able to elicit a motor response is regarded as "motor." The effects of both irritative and destructive lesions are then considered, and the numerous clinical types produced by cortical lesions are fully described. The analysis and descriptions of symptoms of disease, and especially of motor syndromes, are as striking a contribution to the subject as his electrical experiments, but it must be said that his observations diverge considerably in many points from those of others who have studied these problems.

Brouwer writes more concisely but exhaustively on the visual system, and Pfeifer on the auditory radiations and the cortical centre for hearing, touching also on its relation to aphasia and amnesia. The separate chapter on aphasia has been undertaken by Isserlin; every aspect of this important subject, the physiological, anatomical and psychological, are adequately dealt with and the whole is characterized by its clear and critical treatment. The agnosias and apraxia are fully discussed at considerable length from every point of view by J. Lange. Bostroem contributes a short but excellent chapter on the mental symptoms of cerebral disease. In his article on the vegetative system Frank deals with such symptoms as fever, metabolic disturbances and essential hypertension, as well as with those disorders generally attributed to its disease. In the last chapter Kretschmer summarizes his views on the significance of build and on constitution.

Band VII. *2ter Teil. Liquor, Hirnpunktion, Röntgenologie.* S. 553, mit 416 Abbildungen. Price RM. 117.

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Band XI. *Traumatische, Präsenile und Senile Erkrankungen und Zirkulationsstörungen.* S. 548, mit 148 Abbildungen. Price RM. 104.

Marburg opens this volume with a long and valuable article on the traumatic affections of the brain and spinal cord, in which he discusses the origin and nature of cerebral concussion as well as the grosser lesions which result from mechanical injuries. He describes the symptomatology of epidural and subdural hæmorrhages, traumatic softening and œdema, and discusses post-traumatic epilepsy. In addition to mechanical injuries of the spinal cord he deals with those resulting from electrical accidents, and with the relation of trauma to later developing organic disease.

The greater part of the volume is, however, occupied by Hiller's chapter on circulatory disturbances of the brain and spinal cord, in which, in addition to the symptoms of gross vascular lesions, the effects of arteriosclerosis and of disordered circulation on nervous tissue are fully considered. Grünthal contributes a short but excellent chapter on the senile and presenile affections of the brain and spinal cord, including senile dementia and Pick's and Alzheimer's diseases.

Band XIV. *Raumbeengende Prozesse.* S. 417, mit 280 Abbildungen. Price RM. 86.

This volume is wholly devoted to tumours of the central nervous system. Antoni of Stockholm contributes an article on tumours of the spinal cord and its membranes, in which the pathology of the various forms of growth which involve these parts is particularly fully described and well illustrated, but the symptoms they cause and their diagnosis are also adequately discussed. One half of McLean's (of Portland) chapter on intracranial tumours is devoted to their histology, but this is so concisely and clearly written that it will be welcome to clinicians. The incidence of each type of tumour, its clinical course, operability and radio-sensitivity are important features to which the author gives adequate attention. He discusses fully the nature and significance of the symptoms of increased pressure, but the space allotted to local diagnosis is insufficient. The employment of X-rays and other means of diagnosis is again introduced, and there is a short section on operative treatment. McLean has also written on pituitary tumours, including stalk tumours.

The invasion of the central nervous system by animal parasites as cysticercus, echinococcus, distoma, schistosoma and trichina, are fully dealt with by Henneberg, and Wartenberg discusses abscesses of the brain and spinal cord.

Die Bioelektrischen Erscheinungen der Hirnrindenfelder. von A. E. Kornmüller. Leipzig: G. Thieme. S. 118. Price RM. 7.80.

This monograph gives a valuable summary of the author's work on the electrical activity of the cortex, carried out during the past five years at the Kaiser Wilhelm Institute. It deals particularly with the localization of different types of activity, spontaneous or due to sensory stimuli, in areas of different cyto-architecture. In the monkey's cortex, for instance, not only is the response to illuminating the eye confined to the striate area, but there is an abrupt change in the frequency of the spontaneous oscillations in passing from it to the adjacent area 18. Most of the book deals with the brains of rabbits and apes, but there is a short chapter discussing Berger's work on man.

The author is a pioneer in this new method of research on the brain and his book shows what great possibilities it offers for further advance.

Neurological Surgery. By Loyal Davis. London: Henry Kimpton. 1936. Pp. 429, with 172 illustrations. Price 28s.

Dr. Loyal Davis has succeeded in compressing into a relatively small book the whole of neurological surgery—brain, spinal cord, peripheral nerves, and sympathetic nervous system. Comprehensive description of any particular lesion could not be expected, but the text seems to be adequate. The book is addressed to the general practitioner and not to the highly experienced clinician or surgeon, but because it is a personal record, and because Dr. Davis has had extensive experiences in experimental surgery and physiology, there is much of interest. In illustration of the scope of the book the point may be made that only 81 pages are devoted to intracranial tumours, and that whereas seven lines are devoted to colloid cysts of the 3rd ventricle, several pages are devoted to the problem of sympathetic afferents in the perception of pain. Probably the average general practitioner is not particularly interested in either subject but both can be made fascinating, and on the one he has chosen Dr. Davis writes authoritatively and will be read with interest. A similar bias can be discovered elsewhere and would be more remarkable, maybe, if it were absent. A man writes best about that which he best knows. The illustrations are good and descriptions of operative steps have been reduced, very sensibly, to a minimum.

Course of Changes in the Spinal Fluid of Syphilitics. By ESBERN LOMHOLT. *Acta psychiatrica et Neurologica,* Supplementum XI. Copenhagen: Levin and Munksgaard. 1936. Pp. 96.

Since 1920 compulsory notification of syphilis has existed in Denmark, and a careful record has been kept of the subsequent medical history of all syphilitics. These records have enabled the author to trace the course of the disease in a very large number of patients on whom one or more lumbar punctures had been carried out in the early stages. It has thus been possible to assess the prognostic significance of the meningeal reactions which occur in the secondary stage of the disease. This problem has been attacked from two points of view: (1) What proportion of syphilitics develop neurosyphilis? and (2) what were the findings on lumbar puncture in the early stages of the disease in patients who subsequently develop neurosyphilis? From an examination of the available records he finds that while most of the meningeal reactions of the secondary period are ephemeral and without prognostic significance those reactions which persist into the latent period are not so favourable. Thus he could find no case in Denmark, and only one certain case in the literature, in which neurosyphilis developed after the cerebrospinal fluid had been found normal during the latent period. This confirms the experience of Ravaut who found that neurosyphilis is most likely to develop in cases in which the meningeal reactions of the secondary stage do not yield to treatment. Lomholt also found that general paralysis seldom appeared in patients who had received abortive treatment during the primary stage and in whom no secondary exanthem had appeared. But cases in which the spinal fluid was already abnormal during the primary stage might develop general paralysis without passing through a secondary stage. When such far-reaching conclusions are arrived at documentary evidence has a special value, and this evidence is provided in the series of tables and case histories which form the second half of the book.

While the prognostic significance of early changes in the cerebrospinal fluid in syphilis is the most important question dealt with in this monograph, many subsidiary points are raised, and to some of these the author has been able to give fairly definite answers. The Danish records of syphilis are unique and we are therefore specially grateful to Dr. Lomholt for making his analyses of these records available to all.

La Douleur dans les Affections du Système Nerveux Central. Par JULIAN DE AJURIAGUERRA. Paris: G. Doin. Fr. 25.

The time was ripe for the preparation of a monograph dealing with the pathophysiology and clinical analysis of central pain. This difficult subject has been ably approached in Ajuriaguerra's study. Critics may point out that the superstructure of hypothesis balances somewhat precariously on a too slender erection of established data, but this is partly inherent in the nature of the subject-matter. Ajuriaguerra's conclusions probably will not receive universal acceptance, but his arguments and opinions are thoughtful and merit consideration. His clinical material is particularly rich, though many will argue that in dealing with spinal cases of central pain, he has cast his net rather too wide. No reference is made to central pains following herpes zoster, and the author does not refer to psychogenic pains at all fully in discussing diagnosis or pathogenesis.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & CURNOW, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

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CHONDRO-OSTEO-DYSTROPHY OF THE HURLER TYPE (GARGOYLISM). A PATHOLOGICAL STUDY.

BY W. R. ASHBY, R. M. STEWART AND J. H. WATKIN.

Of the syndromes composing the complicated group of congenital osseous dystrophies, not the least remarkable is that which has as its cardinal features mental deficiency, dwarfism, deformity of the limbs, corneal opacities and enlargement of the liver and spleen.

This bizarre combination of clinical signs was first described by Gertrud Hurler, who in 1919 recognized that the features of her two cases represented a unit syndrome quite unlike anything hitherto described. Her account was soon followed by a number of others, often described as isolated instances of unusual clinical cases; but early in 1936 a new impetus to the study of the condition was given by Ellis, Sheldon and Capon, who reviewed the records of ten cases collected from the literature, to which they were able to add seven personally observed. On account of the large head, grotesque inhuman facies and deformed limbs, they suggested for this form of chondro-osteo-dystrophy the name gargoylism.

In the absence of post-mortem material these authors were unable to contribute to the pathology of the condition; but they noted that the microscopical findings in Hurler's first case, subsequently investigated by Tuthill (1934), were such as to suggest the possibility of a general disturbance of lipoid metabolism.

Our present communication is concerned with the pathological investigation of the nervous system and certain visceral organs of two cases. The first of these was a male patient who was shown at the Royal Society of Medicine in 1921 by Jewesbury and Spence under the heading "Acrocephaly with other Congenital Deformities"; the second case was the elder of two sisters, the younger of whom had been the first case described in the series recorded by Ellis and his co-workers.

In both our cases evidence was found not only that this dystrophy was closely allied to the diseases of metabolism in which there is storage of lipoid in the reticulo-endothelial system—the so-called xanthomatoses or lipoidoses—but that, as Tuthill surmised, the histological appearances in the nervous system were very similar to those found in amaurotic family idiocy.

Before describing the pathological aspect of our two cases, it may be useful to review the salient clinical features of the disease.

Bone changes.—Skull: Hydrocephalus has been noted in several cases, but, even when this is not present, the cranium is invariably enlarged, and in shape brachycephalic, scaphocephalic, acrocephalic or mildly oxycephalic. Prominence of the frontal bones and supra-orbital ridges, lateral bossing of the temporal bones and prominent bony ridges in the neighbourhood of the sutures have been described. In three cases there was distension of the frontal veins. The facial portion of the skull may be small in proportion to the large cranial vault, though more often the face is described as being broad and full. The bridge of the nose is almost invariably depressed, and increased inter-orbital breadth is also a characteristic feature. The inferior maxilla is usually strongly developed, while the frequent disclosure by radiography of a marked enlargement of the pituitary fossa is of considerable interest.

Vertebral column: Nearly all subjects present a marked shortening of the cervical spine so that the massive head appears to sit almost directly on the shoulders. With one or two exceptions, all the recorded cases have shown an obvious degree of kyphosis, usually dorsilumbar, but not associated with scoliosis. Spina bifida may be present. The radiological appearances bear a close though not identical resemblance to those found in osteochondropathia multiplex. In both diseases there may be platyspondylosis; irregularity of alignment with backward projection of a lower dorsal or lumbar vertebra; and, very characteristically, a hook line projection on the anterior aspect of the body of one of the upper lumbar vertebræ.

Thorax: The clavicles may be massive and thick. Deformity of the thoracic cage, though never so gross as in Morquio's disease (1929), is usually present. "Trichterbrust," pectus carinatum, Harrison's sulcus, rachitic flare, beading, and expansion of the ribs at their sternal ends have all been described.

Limbs: A certain degree of micromelia is usually present, the long bones being not only shorter but thicker than normal. More characteristic, however, is the limitation of movement, which has its maximum development in the digital joints. The fingers are short and clumsy, and usually show some degree of flexion. In advanced cases flexion at the terminal joints is marked, the finger ends presenting a peculiar hook-like appearance. This condition of claw hand must be considered one of the most distinctive features of the syndrome. The hands are described as being broad and paw-like. The thumb and metacarpophalangeal joints may show no restriction of movement.

Shortening and deformity is much less evident in the lower limbs, but there is usually limitation of movement at the knees, and genu valgum and coxa vara have both been described. Radiographic examination of the limbs shows poorly developed glenoid fossæ and acetabula, with flattened irregular heads to the humeri and femora, and short broad metacarpals and phalanges. Delayed epiphyseal development has been noted.

Teeth.—Various irregularities and defects are found. The incisors may be spaced, obliquely placed, massive or hypoplastic, and sometimes show crescent-shaped notches on their free borders.

Eyes.—Slight ptosis, large thickened lids and internal strabismus have been reported, but the most constant abnormality, and one which must be given a high diagnostic value, is congenital clouding of the cornea. When present the clouding is uniform in both eyes and, as might be expected, its effect on vision varies with its degree. Appearing first as a diffuse haziness which causes little interference with vision, with the passage of time it becomes more pronounced until the cornea acquires an opaque milkiness which reduces visual acuity to perception of light only. The condition is said to be caused by the presence of multiple opacities scattered principally in the deeper layers of the cornea. The pupillary reflexes do not appear to be interfered with. In more than one case an abnormally large cornea has been noted. Another change which may ultimately occur is buphthalmos. In a moderate degree it existed in the terminal stages of the illness of our patient M., and it was a marked feature in two siblings reported by Davis and Currier (1934). Although these authors regarded their cases as examples of Morquio's disease, and although corneal opacities were not specifically referred to, an analysis of their findings leaves little room for doubt that they were in reality dealing with the syndrome now under discussion.

Visceral organs.—Enlargement of both the liver and spleen has been noted on at least ten occasions, while enlargement of one organ alone—usually the liver—occurs almost as frequently. In our two cases, verified by post-mortem examination, neither of these two organs was enlarged.

Facies.—In certain respects the facial appearance resembles both that of the congenital syphilitic and that of the cretin. Even in infancy the features are peculiarly ugly and unchildlike. Congenital syphilis is suggested by the corneal opacity, the snub nose and, when present, the notched incisors; while the full rounded broad cheeks, thick everted lips and a partially open mouth are reminiscent of cretinism. In several of the recorded cases competent observers have made a diagnosis of hypothyroidism.

In nearly every case the eyebrows have been described as coarse and heavy, often contrasting with the hair on the scalp. On the latter it may be fine and silky, or coarse and wiry, but seldom scanty. The ears are usually low and obliquely placed.

Tongue.—The tongue is usually described as being large and at times protruding, as in the second case reported by Hurler (1919). In the case, the clinical history of which is given at length in this paper, the tongue was not only large but exhibited fissuration and prominent papillæ very much like that of the Mongol.

Skin.—On the face the skin has been described as soft and rosy, while on the body it may be pale, muddy, sallow, and dry. Hurler noted that the skin on the chest could be lifted up in folds, and that cushions of fat were present in the mammary region and on the abdominal walls. It is perhaps more than a coincidence that in several cases the weight at birth has much exceeded the normal. A marked lanugo may be found on the face, trunk and limbs. In one case a marked degree of hypertrichosis was present on the lower limbs.

Muscular system.—Though actual wasting has not been observed, the musculature is usually poorly developed, especially that of the abdomen. A marked degree of abdominal distension is a very frequent finding, and, in two cases, diastasis of the recti was present. Umbilical, and, less frequently, inguinal herniæ are also characteristic features.

Nervous system.—No gross abnormality has been recorded except in the cases reported by Davis and Currier. Their two siblings developed optic atrophy, and, in the elder boy, an encephalogram showed symmetrical dilatation of the lateral ventricles with slight enlargement of the third ventricle. Several of the cases reported could stand only with assistance, but it does not appear that any true motor paralysis exists.

Mental state.—From the published reports it is a little difficult to assess the exact mental status of the recorded cases, but as a rule some degree of mental retardation is present. The majority of the subjects have been young children and few have progressed beyond the stage of low grade imbecility. Speech was either not acquired at all, or was limited to the utterance of a few words. Habits of cleanliness were acquired only by a few. Of the seven cases described by Ellis, Sheldon and Capon (1936), their first, a female dwarf of 18, was the most intelligent. She learnt to speak a few words, to understand simple requests, and to acquire clean habits. The same authors refer to the possibility of mental regression, and this is borne out by the clinical history of our patient. In 1921, at the age of 5½ years, he was clean in his habits, could speak, and although his intelligence was limited, was by no means an idiot. Fifteen years later he had sunk to the lowest grade of amentia, and was in fact a typical idiot, noisy, resistive and completely inaccessible.

These patients are for the most part of friendly disposition, docile and obedient and usually inactive, being content to lie quietly in bed. In the majority the ability to walk is acquired late. In the two cases reported by Davis and Currier "Intelligence seemed to be unimpaired," but we are not told whether their mental state was investigated by the application of special tests. Nevertheless, the possibility of normal mental development has to be envisaged. Nonne (1924) refers to three sisters who were intelligent, and, through the kindness of Dr. Orr-Ewing of Bristol, one of us has had the opportunity of examining two brothers whose degree of mental retardation was so slight as to be almost completely masked by their specious brightness : yet otherwise they were both extremely typical gargoyles.

Other features.—Some stress is laid by Ellis and his co-workers on the presence of rhinitis, but it is by no means constant. For the most part biochemical investigations have proved negative; only in one case has the possibility of defective liver function been suggested by a slightly abnormal lævulose tolerance test and a high blood glycogen. The formed elements of the blood show no abnormality. Sexual development appears either to remain infantile, or be in harmony with the stage of physical development reached. Extreme sexual infantilism was however present in the first case of the series reported by Ellis and his co-workers. The heart, lungs and urine are usually normal, and no abnormality of thyroid, thymus or lymphatic glands has been detected during life. In Case 2 of this paper a marked degree of mitral stenosis was present. Constipation does not appear to be a prominent feature, but a tendency to respiratory infection is fairly common.

Family history.—Almost invariably the parents are healthy and consanguinity is exceptional.

REPORT OF CASES.

Case 1.—S. M., aged 19, was admitted to Leavesden Hospital on November 2, 1934.

Family history.—Apart from a history of nervous breakdown in the father, a railway porter, the family history was satisfactory. A blood Wassermann reaction made on the parents was negative in each instance.

Past history.—The patient is the elder of two male children, the second, aged 15, being normal and in employment as an office boy. During pregnancy the mother endured mental stress, and there was protracted pressure and asphyxia at the birth of the patient, which was aided by instrumental delivery. At birth he weighed 12 lb., and was said to have had a repulsive appearance, being born with a deformed skull and a film over both eyes. Teething was normal but there was considerable delay in learning to walk and talk, neither function being acquired until after the fourth year. Speech never went further than the acquisition of the language of infancy. He acquired cleanliness in habits and was able to feed himself.

In infancy he suffered from measles, and received out-patient treatment for his eye condition. This, however, did not prevent him from seeing fairly well, as the mother stated that he ran about without bumping into things. He was never able to use his right upper limb to the same extent as his left. He was a heavy child, and, on the supposition that he suffered from thyroid deficiency, thyroid extract was administered over a period of two years. No apparent benefit was observed, and the mother finally discontinued the treatment because she thought it was making him violent.

When in his 5th year he was shown by Jewesbury and Spence (1921) at the Royal Society of Medicine, Section for the Study of Disease in Children. He was then of normal weight and height, but presented a curious appearance. His face was "full-moon" in shape, the bridge of the nose depressed, the eyeballs prominent, the head brachycephalic, the corneæ cloudy, and the hands in a condition of "claw fingers." Examination of the blood, urine and cerebrospinal fluid gave negative results. Sugar tolerance was normal. On radiographic examination the pituitary fossa was noted to be twice its normal length but without evidence of erosion or absorption. The metacarpals and phalangeal bones were irregular in shape, the proximal phalanges tending to be cone-shaped and the terminal phalanges being smaller than normal. Radiographic examination of the other parts of the skeleton failed to reveal further abnormalities.

In 1922, when 7 years of age, he was examined and deemed to be mentally defective. He was admitted to a special school, but made only twenty-four attendances. In conduct he was restless and spiteful, never still, and constantly interfering with other children. He made no educational progress whatever, and, when re-examined in January, 1923, was graded as imbecile (fig. 1). Thereafter he remained at home, showing little change until his 17th year, when it was noticed that he was becoming weak on his legs. About this time he fell on the back of his head, and was apparently unconscious for about a quarter of an hour. According to the statement of his mother, within three days of this accident he was unable to walk at all and became almost completely blind. After a period of institutional care in St. John's Hospital he was certified under the Mental Deficiency Acts.

Examination.—The patient is dwarfed in stature, with cretinoid features and generally repulsive in appearance. Height, 4 ft. 2 in.; weight, 5 st. The head is rounded with flattening in the occipital region, large in proportion to the size of the body, with closed fontanelles and no evidence of bossing. It has the following measurements: Height, 158 mm.; length, 183 mm.; breadth, 153 mm.; circumference, 56·7 cm.; cephalic index, 84. The hair on the scalp is coarse and dry, dark in colour and sparse. The eyebrows are heavy and strongly arched. The eyes are large, prominent, widely set and show a moderate degree of buphthalmos. On both sides the cornea is a milky white colour, the degree of clouding being evenly distributed and diffuse, but not sufficiently marked to obscure completely the outline of the blue iris beneath. The pupils react a little sluggishly to light and visual acuity appears to be much reduced. It was not possible to see the discs.

The nose is flat and broad with depressed bridge and nostrils which look forwards as well as downwards. There is no nasal discharge.

The lips are thick and everted, the tongue large and protruding with well-marked circumvallate papillæ and some degree of fissuration, though less pronounced than that seen in a Mongol. The palate is highly arched; the upper central incisors show a trace of notching at their free edges but are not peg-shaped, the condition of the permanent teeth is fair and the lower jaw fully developed.

The face is large and broad with pale flabby cheeks and large ears set rather low.

The neck is remarkably short and thick, the thorax wide, with flaring of the costal margin: a marked Harrison's sulcus is present.

The abdomen is large, protuberant, and shows the presence of a small umbilical hernia.

The skin of the trunk is coarse and dry with a marked excess of coarse hair on the buttocks and legs.

Sexual development exceeds the normal.

Both upper limbs are short with limitation of movement at the elbows and joints of the fingers. The digits are short, especially their terminal phalanges, and the terminal interphalangeal joints are acutely flexed in a remarkable hook-like way. The right thumb is flexed, the left extended. The lower limbs are in proportion to the size of the trunk; they are extended and show a moderate degree of rigidity at knee and hip joints; the feet and toes are large in proportion to the size of the legs but show no abnormality in posture. No kyphosis is present.

The thyroid, liver and spleen are not palpable, and examination of the lungs and heart reveals no abnormality. Pulse 108, blood-pressure 136/50 mm. Urine normal. The Wassermann and Meinicke reactions are negative.

Abdominal reflexes present. Plantars: flexor response. Arm and knee jerks brisk. He is unable to sit, stand, or walk, but retains considerable power in his limbs, clutching at people within reach with a surprisingly firm hold.

Progress.—The patient was confined to a chair from which he made no effort to move, or to interest himself in his surroundings. He was extremely resistive, difficult to feed (spoon feeding usually occupied twenty minutes), and faulty in habits. He often uttered a plaintive harsh cry, but was not observed to shed tears. "Bread," "Mummy," and "Daddy," were the only words he was heard to say. When asleep his breathing was always noisy and snoring.

One month after admission he developed an attack of bronchitis, and the thyroid treatment which had been commenced on his admission was discontinued. His illness lasted a fortnight and he appeared to be making a good recovery. On the evening of April 26, 1935, however, he suddenly collapsed in his chair, and all efforts to revive him proved unsuccessful.

Post-mortem examination.—An autopsy performed sixteen hours after death revealed large persistent thymus; thyroid of normal size, firm and with well-defined isthmus; heart small but otherwise normal; bilateral pulmonary congestion; liver weight 960 g., capsule thickened and marked decrease in bulk of left lobe; on section, slight fatty change. Spleen, weight 100 g., of normal consistence and appearance. Kidneys and suprarenal glands normal. The pituitary gland lay in a much widened sella turcica, and was enlarged to almost twice the normal size, both lobes sharing in this enlargement.

The inner and outer tables of the calvarium were thickened and dense, with obliteration of the diploë. The metopic suture was not closed throughout its whole length. The brain was of normal consistence, and, after fixation in 10 per cent. formol saline weighed 1043 g. Right cerebral hemisphere 495 g. Left cerebral hemisphere 393 g. Cerebellum 155 g. The cerebral hemispheres were asymmetrical; the left was broader and flatter than the right, and had on its surface a large area of cortical atrophy covered by thickened and opaque pia-arachnoid. The lesion occupied the stem of the Sylvian fissure, part of the inferior frontal, and the lower halves of the pre- and post-central gyri.

The right cerebral hemisphere showed two small areas of thickened pia-arachnoid, but without cortical atrophy—one occupying the horizontal ramus of the Sylvian fissure and the other in the prefrontal region. On both hemispheres the convolution pattern was somewhat simple.

On division of the two cerebral hemispheres a condition of unilateral hydrocephalus was revealed. The left lateral ventricle showed a very marked degree of ventricular dilatation affecting all its area. Save for a small area overlying the caudate nucleus there was no evidence of ependymitis. Attached to the choroid plexus in the body of the ventricle was a small, firm, rounded tumour about the size of a hazel nut. From its position it was obvious that the foramen of Monro could not have been blocked. Another tumour occupying the same position, and of the same size, was present on the choroid plexus of the otherwise normal right lateral ventricle. A vertical coronal section through the left cerebral hemisphere in the plane of the middle commissure showed that the area of softening was sharply confined to the cerebral cortex in the region described above, with, however, marked thinness of the underlying white matter. On this side, too, the basal ganglia were much smaller than on the opposite and normal side.

The cerebellum was symmetrical with a normal fourth ventricle. Both pyramids, especially the left, were poorly developed; the vertebral arteries were large but otherwise normal.

Microscopic examination.—Pituitary: The morphological appearance of the anterior lobe cells suggested a normal gland which had undergone a general cell hyperplasia. There appeared to be a full complement of acidophile and basophile cells, and possibly some increase in the number of chromophobe cells, but differential counts on serial sections were not attempted. The posterior lobe, though large, showed no abnormal structure.

Thyroid: In all sections the appearances were those of a fœtal type of gland, the tissue consisting almost entirely of masses of cells, some solid and others showing a scarcely distinguishable lumen (fig. 2). Here and there colloid, which stained with basic but not acid dyes, could be seen as small droplets. A few vesicles showed almost normal colloid storage. The epithelium tended to be columnar rather than cuboidal, and to desquamate.

Thymus: The normal structure was preserved. Hassall's corpuscles were present.

Suprarenal: No evidence of disease was found.

Tongue: anterior third. The papillæ were hypertrophied and covered by a much thickened and folded epithelium. Some inflammatory infiltration was present in the muscular tissue beneath.

Tumours of choroid plexus: Both tumours consisted of a loose stroma of fibro-myxomatous tissue in which were large quantities of rounded bodies resembling corpora amylacea. The blood-vessels showed thickening of the media and adventitia, and in places there was a cellular infiltration, the cells consisting chiefly of lymphocytes.

Microscopic examination of nervous system.—Celloidin sections of various cerebral convolutions and of the basal ganglia, pons, cerebellum, medulla oblongata and optic nerves were stained with hæmatoxylin-eosin, cresyl violet and Loyez's myelin sheath stain. Frozen sections from various regions were stained with Scharlach R, Nile blue, Bielschowsky's and Holzer's methods. Tissue mordanted in 2 per cent. bichromate of potassium solution was stained by the methods of Marchi and Wolters. For the identification of deposit in certain areas special staining methods were adopted.

Nerve cells: Low power examination of the cerebral cortex showed a considerable disturbance of the cyto-architectonics, the normal columnar arrangement of nerve cells being often lost, and many cells displaying a loss of their normal polarity. The average thickness of the cortical grey matter was slightly less than normal, the reduction being most evident in the supragranular layers.

In the region of the cortical scar on the surface of the left cerebral hemisphere no ganglion cells could be identified. Elsewhere the ganglion cells throughout the cerebrum, cerebellum, pons, medulla and spinal cord showed, with great uniformity, distinctive changes of a type not usually encountered in the brain of the ament. In general, these bore a striking resemblance to the appearances found in amaurotic family idiocy.

The cell bodies were swollen, pear shaped or spherical, the nucleus pushed to one side—usually towards the apical dendrite—and often shrunken or pyknotic, the nucleolus being conspicuous and the Nissl substance reduced in amount. Occupying the cytoplasm of the basal portion of the cell a granular substance formed a conspicuous mass, which in frozen sections stained readily with appropriate stains (fig. 3).

Swelling of dendrites was nowhere a conspicuous feature, though in some localities they showed an abnormal affinity for aniline dyes which enabled them to be visible some distance from the cell body; they did not appear to be noticeably fewer than normal. In cresyl violet preparations some of the larger nerve-cells showed an endocellular network replacing the Nissl substance, and Bielschowsky preparations frequently revealed a dislocation of neurofibrils to the cell periphery, this change being apparently due to the infiltrating substance. Here and there ghost-like outlines of cells in the process of disintegration could be observed, but, side by side with abnormal cells, were others in which little or no departure from the normal could be detected. The Betz cells, those of the hypoglossal nucleus, and many of the larger motor cells in the anterior horns of the spinal cords, were less affected than the medium and large pyramids of the cerebral cortex. Cellular changes of a very similar character to those found in the medium pyramidal cells also existed in the basal ganglia, but in the optic thalamus the granular deposit filling the large cells was coarser and more conspicuous than elsewhere.

A comparison of the foregoing cell changes with those found in amaurotic idiocy showed an obvious similarity, though the extreme degree of ballooning, distending a cell to perhaps three times its normal diameter, was not seen, nor was the degree of involvement of the cell processes as great as in Tay-Sachs' disease.

Though no part of the nervous system existed without the presence of altered nerve-cells containing a granular deposit the cellular reactions were more marked in some situations than in others. Thus in the cerebral cortex the deeper lying pyramids appeared more involved than those near the surface, and profoundly altered cells were particularly numerous in the optic thalamus, the mid-brain, the dentate nucleus of the cerebellum and the inferior olives of the medulla.

Staining reactions of the granular deposit in nerve-cells.—In unstained sections a very faint yellow tinge could sometimes be discerned in the cytoplasm; usually, however, the granules were colourless. In sections of cortex stained with Scharlach R the deposit acquired a pale orange red colour; in the cells of the optic thalamus the colour was a deeper red. With Nile blue a dark blue colour was obtained; with thionin and toluidin blue a greenish yellow coloration; and with cresyl violet a dark purple. Pyronin methyl green gave a very fine differential staining of nerve-cells. The nucleus and Nissl substance stained lilac, the nucleolus dark red and the granular substance a brilliant green. For the identification of the granular substance hæmatoxylin stains proved less satisfactory, but as a rule the granules stained a brownish black. Marchi's method failed to impart any colour. The method of Loyez gave a bluish black. Gram's stain gave no differential staining. The appearances in Bielschowsky preparations varied; in some cells a reticular formation of the cytoplasm with a dark periphery of neurofibrils could be seen; in others the expanded cell bodies appeared to be occupied by fine dust-like granules.

Frozen sections mordanted for two days in bichromate solution gave the deposit in some nerve-cells a faint brownish colour, and, with four days mordanting, the colour darkened to a brownish black. Some cells remained unaffected.

In the cells of the zona compacta of the substantia nigra it was possible to identify both the normal melanin pigment and the abnormal lipoid substance which was found in all the nerve cells of the brain.

It was noteworthy that even in ganglion cells which had preserved their normal contour and size appropriate staining methods seldom failed to reveal the presence of the intracellular deposit.

Cerebellum.—Changes in the cerebellum were inconspicuous. Purkinje cells showed distortion in shape owing to the presence within them of the granular deposit, but on the whole they were well preserved and had not suffered numerical loss except in a few folia. The folia seemed finer and more delicate than normal, the molecular and granular layers being reduced in width and the cells in the latter clumped into tigroid masses. In Bielschowsky preparations normal basket fibres could be detected.

Nerve fibres.—In spite of the marked changes in the cell bodies the nerve fibres and their myelin sheaths were well preserved. In a few cortical areas the tangential fibres appeared less dense than normal; otherwise satisfactory staining was found in all areas.

Neuroglia.—In the area of the large cortical scar there was a marked excess of fibrous glia, but in nearly all other cortical regions the changes were slight. The occipital cortex was exceptional in showing a marked overgrowth of fibrous glia in its outermost lamina.

Much more striking were the changes in the basal ganglia. Beneath the ependymal surface of the caudate nucleus, in the optic thalamus, and in the hypothalamus rostral to the plane of the mammillary bodies, there was a marked gliosis; gliosis also existed beneath the ependyma of the floor of the fourth ventricle.

In several localities proliferated oligodendroglia, forming long chains, could be seen in the white matter.

In two localities—the prefrontal and precentral cortex—compound granular corpuscles were present in the subcortical white matter. Within microglial cells the infiltrating substance was found in one or two sections only, but, in a limited number of areas, numerous masses and droplets of a peculiar lipoid-like substance were found lying free in the tissues. These are described below.

Mesodermal tissues.—No abnormality of the pia-arachnoid was found except on the area of cortical scarring where it contained numerous fibroblasts, lymphocytes and particles of yellow pigment.

Blood-vessels.—The basilar, vertebral and internal carotid arteries were healthy. Many of the smaller vessels of the lenticular and caudate nuclei and of the optic thalamus were surrounded by droplets of the lipoid substance already referred to. The staining reactions and solubilities of this deposit appeared to differ in certain particulars from any hitherto recorded. They therefore merit a full description.

Lipoid deposit.—In unstained brain tissue the actual lipoid substance was invisible to the naked eye, but its situation was revealed by polarized light, the droplets showing up as dazzling points of white light against a black background. The size of the masses varied. Very often they appeared as minute drops, about 20 to 30μ in diameter, closely aggregated round vessels and not diffusely scattered throughout the tissue. Often the fusion of separate masses gave the appearances of complete rings or masses in the adventitial spaces of vessels. Mulberry-like masses with blurred margins were also present. Evidence of inclusion of this substance within cells was scanty. Possibly a few microglial cells of the putamen contained small droplets, though on this point it was difficult to be certain as almost all the material lay free in the tissues and may have been lying on rather than within these cells. Only in one or two sections could the material be seen within the lumen of blood-vessels.

Staining reactions.—The behaviour of the lipoid substance to different stains was as follows :—

Acid dyes: It remained unstained by acid fuchsin, brilliant green, Congo red, eosin, light green, orange G, van Gieson. *Basic dyes*: cresyl violet, rose red ; methyl violet, colourless , mucicarmine, rose red ; neutral red, orange red ; safranin, orange yellow ; thionin, lilac, red or yellow ; toluidin blue, lilac. *Natural dyes*: Hæmatoxylin, light blue. *Methods*: Bielschowsky, unstained ; Giemsa, rose red ; Holzer, unstained : iron hæmatoxylin, black ; Loyez, unstained ; Marchi, unstained ; Nile blue, unstained ; Scharlach R, unstained ; Unna-Pappenheim, unstained.

For neutral red this substance had a special affinity, the appearance in celloidin sections being that of brilliant orange red droplets. With aniline blue as a counterstain an even more effective picture was obtained, the deposit standing out with unusual distinctness against the dark blue background.

Solubilities.—Frozen sections which had been dried were immersed in different fluids at room temperature for about ten minutes, after which they were again dried and then examined in water with polarized light. The lipoid deposit behaved as follows : (*a*) cold water, insoluble ; (*b*) absolute alcohol, insoluble ; (*c*) acetone, insoluble ; (*d*) ether, insoluble ; (*e*) benzene, insoluble ;

(*f*) chloroform, partly soluble; (*g*) hot chloroform, totally soluble; (*h*) hot xylol, totally soluble; (*i*) chloroform and methyl alcohol, equal parts, totally soluble; (*j*) boiling absolute alcohol, totally soluble.

The results were perfectly clear cut: either the deposit disappeared in a few seconds or it remained totally unaffected. The only exception was with chloroform, in which the brilliantly shining mass faded rapidly to a pale white haze which did not alter with further immersion.

Melting point.—When watched on a hot stage, the masses showed clearing and loss of double refraction when the water in which they were observed was just on the point of boiling.

Distribution.—The deposit was most abundant in the globus pallidus (fig. 4) and in diminishing amounts in the putamen (fig. 5), caudate nucleus, optic thalamus, zona reticulata of the substantia nigra and dentate nucleus of the cerebellum (fig. 6). In the cerebral cortex it was found only in two localities—the pre- and post-central cortex. A small amount was also found lying in the grey matter of the cerebellar hemispheres, and in one or two situations actually free between folds of pia mater covering the folia. The substance was not found in the white matter of the cerebrum and cerebellum.

Although no difficulty was experienced in locating even minute masses with the aid of polarized light, a remarkable and puzzling feature was the fact that it could not be identified when frozen or paraffin sections were stained by any of the ordinary acid or basic dyes. Only when stained celloidin sections came to be scrutinized was it possible to identify the material. That it should not be seen on paraffin sections was to be expected since being soluble in hot chloroform and xylol it would have been removed in the process of embedding but its failure to appear in frozen sections raised the question whether the treatment incidental to the celloidin method of embedding had in some way converted a normally unstainable substance into one which readily took certain basic dyes. To this question we shall return later.

CHEMICAL ANALYSIS OF BRAIN CORTEX AND WHITE MATTER.

Our estimations were limited to the determination of the total lipoid, cerebroside and water values.

Methods.—A block measuring about 1½ by 1 by 1 in. was removed from the medial surface of the left frontal lobe anterior to the rostrum of the corpus callosum, freed from membranes and cut into slices. From each slice grey and white matter were separated, the border line between the two being avoided. Analyses were then made using a slight modification of the procedure previously described by one of us. For purposes of control material was obtained from the brains of three psychotic subjects who during life presented no evidence of neuronic degeneration.

The results of the analyses are given in the following table.

	Per cent. cerebroside				Per cent. water	
	Cortex		White matter		Cortex	White matter
	Dry	Wet	Dry	Wet		
Patient M.	1·74	0·250	5·15	1·32	85·6	74·4
Control 1	3·09	0·505	4·89	1·48	83·7	69·8
Control 2	2·91	0·490	6·41	2·10	83·1	67·2
Control 3	2·77	0·491	5·61	1·89	82 3	66·3

Case 2.—A. W., a female child, aged 3 years, was admitted to Tooting Bec Hospital on June 13, 1918. She was one of three siblings, the offspring of healthy parents. Her younger sister who suffered from the same condition was reported in the series collected by Ellis and his co-workers. The defect was said to have been present from birth.

State on admission.—Height 30 in. Weight 26 lb. The patient was a well-nourished child with a large head, brachycephalic in conformation. Measurements of cranium (April, 1921): Circumference, 19 in.; length, 7 in.; breadth, 6¼ in.; height, 3⅝ in.; cephalic index, 89. Eyebrows prominent and strongly marked, nose short, with depressed bridge and nostrils directed forwards as well as downwards. Epicanthus. Pupils normal. Angular deformity of the spine. Small umbilical hernia.

The mental state was one of idiocy, the patient being listless, unable to stand, incapable of articulation and dirty in habits. A photograph taken about this time shows a round-faced child with a heavy expressionless face, not, however, typical of the gargoyle. Three years later there was a marked alteration. The features were now peculiarly unchildlike, and unmistakably those of the type. The increased weight and general appearance of the patient had led to a diagnosis of cretinism; and thyroid treatment had been employed, but without improvement. The condition of the cornea was not mentioned. In 1924 she succumbed to congenital heart disease, aged 9 years.

Post-mortem examination: thirty-six hours after death.—The body was that of a well-nourished girl. Œdema of extremities and umbilical hernia were present. Bossing of the frontal and temporal regions was noted, and a photograph of the base of the skull taken by Dr. T. Brushfield showed a sella turcica much enlarged in all its dimensions. The dura mater was considerably thickened, the pia-arachnoid congested. The brain was large, soft, simply convoluted, and the cerebellum disproportionately small.

Weight of brain unfixed was 1077 g.; after twelve years' immersion in formalin it weighed 927 g. The right cerebral hemisphere was 408 g., the left 412 g. The cerebellum and brain-stem weighed 107 g. The lungs were congested. The heart weighed 4½ oz.; there was mitral and tricuspid congestion and hypertrophy of the left ventricle. The liver, which weighed 567 g., was firm, congested, and relatively small. The spleen was of normal size. The kidneys weighed 85 g. and showed fœtal lobulation. The thymus was persistent and the size of broad bean. The thyroid was large.

Microscopic examination.—Thyroid: Changes of a striking character were evident. The vesicles were of medium size, and many of them were broken down or running into each other. Some were partly filled with small masses of colloid, staining darkly with hæmatoxylin. The cells lining the alveoli were either low, cubical or flattened. The stroma was in great excess, giving a picture of marked fibrosis, and the whole appearance was that of a glandular structure which had undergone a considerable degree of parenchymatous atrophy (fig. 7).

Liver: Only paraffin embedded material was available for study, and in sections stained with hæmatoxylin and eosin there was evidence of slight degree of fatty change and of chronic venous congestion. No foam cells could be found.

Nervous system: The cerebral convolutions were of normal pattern with no evidence of wasting. There was no asymmetry and no evidence of hydrocephalus. Both pyramids were poorly developed, but the olivary bodies were unusually prominent. On the mesial surface the splenium of the corpus callosum and the pulvinar seemed unusually exposed.

The brain had unfortunately suffered by its prolonged immersion in formalin, and, when cut into slices, showed a tendency to develop countless small fissures, so that successful manipulation of frozen sections was a matter of great difficulty. Furthermore, microscopic examination of the cortex gave every indication of post-mortem artefact.

Changes quite unlike those known to occur in any pathological state were present in the ganglion cells; they showed fragmentation and partial disappearance of the cell bodies, with contrastingly well-preserved swollen nuclei. In many situations the latter were covered with granular incrustations. In spite of these difficulties, which were chiefly confined to the cerebral cortex, it was possible to find areas relatively free from post-mortem artefact, and in these small accumulations of intracellular deposit were found within the nerve cells. Except in one or two localities this was insufficient to cause either ballooning of the cell body or displacement of the nucleus. With Scharlach R the inclusions stained a feeble yellow, but with Nile blue nerve cells containing dark blue granules were seen in every region studied. These changes were least evident in the cerebral cortex, and most marked in the groups of large cells within the optic thalamus (fig. 8) and in the cells of the inferior olivary nuclei. In the latter the changes were just as marked as in Case 1, ballooning of the cell bodies being pronounced. As in the first case, the cell processes were relatively well preserved.

The Purkinje cells showed little alteration, but the cells of the granular layer were reduced in number. In four cortical regions the cellular richness of the individual laminæ was much below the normal.

The Betz cells and the cells of the substantia nigra and hypoglossal nuclei were well preserved.

No free lipoid-like deposit could be identified with polarized light, but in view of the age of the material it was not thought worth while making a prolonged search for its presence.

As in Case 1, Holzer's stain disclosed a marked degree of gliosis in the optic thalamus and in the region of the paraventricular nucleus of the hypothalamus. In this case, too, gliosis existed beneath the ependymal lining of the floor of the fourth ventricle. In addition, gliosis was present in the region of the olives where it was not found in Case 1.

DISCUSSION.

As far as we are aware in only one previously reported case has it been possible to record the pathological findings. This was in the first of the two patients reported by Gertrud Hurler, and the histological examination was made by Tuthill, who until his report had been completed did not apparently appreciate that the case he was dealing with was one of osseous dystrophy. The title given to his paper was "Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations and Tuberculomas," and, for this reason perhaps, it failed to attract the attention which its importance merited.

Summarizing the chief pathological findings in his case, it may be said that the architectonics of the cortex were undisturbed save in the region of the tubercles and in the temporal lobe near the cornu ammonis where there was a loss of cells in the third layer.

Changes in the ganglion cells involved all parts of the cortex; balloon-shaped cells, slight puffing of the dendrites and axons, and complete absence of Nissl bodies were observed. The cytoplasm had the appearance of a net-like substance owing to the presence of granules which stained a dark blue with toluidin blue, black with Weigert's myelin stain, and yellowish red with Scharlach R. Cells in all degrees of morphological change contained an infiltrating substance. The cellular changes were particularly marked in the basal ganglia and in the brain-stem, but slight elsewhere. In the white substance of the hemispheres thinning of the myelin sheaths was universal. The optic nerves showed a complete loss of myelin. The cortical glial cells were increased in size, but not in number; and near the larger vessels cells containing lipoid could be seen. Lipoid-containing cells, similar in size to oligodendroglia, were scattered sparsely throughout the white matter and a few areas contained typical fat granule cells.

In the cerebellum, brain-stem and spinal cord the vessels showed a moderate adventitial increase, but in the centrum ovale and basal ganglia the adventitia was developed to an extraordinary degree: in some situations it appeared to be twice as wide as the vessels themselves, being composed of a fibrous network in which were many nuclei. Fine and coarse blue-staining granules were present in the adventitial spaces, around nerve and glia cells, and in masses in the meninges. Although readily stained with thionin they were scarcely visible with hæmatoxylin-eosin and not at all with van Gieson's stain. Only the nuclear aniline stains brought them into view—and only in alcohol-fixed material was it possible to stain them.

The tubercles present lay open to the meninges and were typical of tuberculous disease.

Discussing these changes, Tuthill gives it as his opinion that the enormous growth of the adventitia represented an attempt to absorb the blue staining granules which had accumulated in the perivascular spaces. The possibility that the latter—found only in alcohol-fixed material—were artefacts, is dismissed in favour of the view that they must have originated in the spinal fluid, it being pointed out by Tuthill that they were observed only in the meninges and the perivascular and perineural spaces. Such an explanation, however, is not likely to command general acceptance, though it is not suggested here that this granular substance was an artefact due to the method of fixation for, as will be seen, the lipoid-like substance found in our first case was not dissimilar in its behaviour to certain agents for fixation and embedding.

Comparison of the histological changes with those of amaurotic idiocy.—Amaurotic family idiocy is one of the few diseases of the nervous system which can be recognized with absolute certainty by an examination of the nerve-cells, and, in our first case, their morphological appearances in every area were sufficiently arresting to leave no doubt as to the correctness of Tuthill's observation that in this peculiar disease the changes in the nervous system bear a very close resemblance to those encountered in the juvenile type of Tay-Sachs' disease.

It may be recalled that in this type of amaurotic idiocy, the cell changes, as Spielmeyer (1908) and Vogt (1907) showed, never assume the striking character of those seen in the infantile form. Cytoplasmic distension of marked degree is most exceptional, and degenerative changes in the dendrites and axis cylinders are inconspicuous. Rather is there a limited degree of ballooning of the cell body with slight swelling of the cell processes. Usually there are many normal nerve-cells and the myelin sheaths are but little affected. These changes were well seen in the cases under discussion. In the cerebral cortex swollen nerve-cells showing partial loss of Nissl substance, and distension with a granular cytoplasmic inclusion, were everywhere in evidence. The small nerve-cells and the giant Betz cells were relatively well preserved, the medium and large pyramids showing the most change. Structural changes in the basal ganglia were equally pronounced and reached their maxima in the optic thalamus where evidence of cell destruction was more pronounced than in any other region.

This intensity of the degenerative process in the cells of the optic thalamus has been noted by Hassin (1924) in both the late infantile and juvenile types of Tay-Sachs' disease; it is also a peculiarity of this nuclear mass that the deposit within the cytoplasm of the nerve-cells exists as granules larger, coarser and more intensely stained with Scharlach R than those in other regions. Other parts of the brain in our first case in which ballooning of nerve-cells was marked were the prefrontal cortex, the mid-brain, the inferior olives and the ventral horns of the spinal cord. No accentuation of the process was seen in the occipital region.

In the cerebellum few of the Purkinje cells had escaped, and in some folia they had suffered an actual reduction in number. Though no appreciable degree of atrophy was apparent to the naked eye, sections of the lateral lobe and vermis showed in the granule layer a delicacy of structure indicative of a slight degree of cerebellar atrophy. In this relative integrity of the cerebellum the histological features showed a departure from those seen in juvenile amaurotic idiocy.

The staining reactions of the intracellular substance bore a close resemblance to those encountered in Tuthill's case, and in the now well-known juvenile type of Tay-Sachs' disease. Secondary degeneration implicating the myelin sheaths was almost entirely absent, sections staining well by the methods of Loyez and Weigert.

Gitter cells were seen in two areas, but the heavy mantle of fat granules described by Tuthill as surrounding the demyelinated optic nerves was not seen, the appearance of these nerves being in every way normal. In addition to gitter cells evidence of glial reaction of a more chronic character was found. This was curiously patchy in its distribution and without any obvious relation to the degree of nerve-cell degeneration. Holzer preparations showed that this consisted of a dense interlacement of fine glial fibres and that it was most evident in the optic thalamus.

The nervous tissue from our second case was unfortunately in an unsatisfactory condition for microscopic study, but in spite of post-mortem influences it was possible to determine the presence of the characteristic abnormal substance within the nerve-cells. The impression given, however, was of a much earlier stage in the process, only a few of the nerve-cells showing marked swellings. This is what might have been expected as the patient succumbed to valvular disease of the heart in her ninth year.

The lipoid deposit free in the tissues.—Considerable interest attaches to the finding of an anisotropic lipoid substance in the cerebral cortex, basal ganglia, mid-brain and dentate nucleus of the cerebellum. Without isolation and chemical analysis it is obviously impossible to state with confidence what the substance was, but such evidence as there is suggests that it was composed mostly of cerebrosides—phrenosin or kerasin or a mixture of both. Only in relation to its solubility in cold chloroform is there any doubt. All the known lipoids are completely soluble in chloroform, but this substance did not entirely disappear with this treatment. None the less, from our limited analysis it is possible to exclude certain substances commonly found in degenerative conditions of the nervous system; lecithin and kephalin by their melting point and by their solubility in alcohol; sphingomyelin by its solubility in benzene, cholesterol by its solubility in acetone, alcohol and ether; and lastly cholesterol esters by their property of staining with Scharlach R.

Collections of material, usually designated lipoid or pre-lipoid, have been noted by numerous observers in the late infantile and in the juvenile forms of amaurotic idiocy, but those have invariably stained with scarlet red. It is therefore obvious that there can be no likelihood of their identity with the material under discussion. In its behaviour with certain stains this substance had some points of similarity to the deposits of mucin or mucin-like bodies which have been found in the central nervous system by Grynfeltt (1923), Lhermitte (1924) and others. Like mucin, it showed a special affinity for Mayer's mucicarmine mixture, and like mucin it stained a light blue with hæmatoxylin. With neutral red and with safranine the staining qualities were also those of mucin.

A further point of resemblance lay in the influence which alcohol exerted on its stainability. It was only in celloidin sections that staining with the ordinary basic dyes took place, a peculiarity shared by mucin. According to Hiroisi and Lee (1936) though mucin will stain feebly in frozen sections, alcohol exerts a favourable influence on its staining properties, as it is found much more readily in pyroxylin sections. Whether the grape-like areas of Buscaino (1920) are artefacts of autolytic origin, or products of mucoid degeneration, has not been finally settled; but their behaviour with stains is very like that of mucin, and under certain conditions doubly refractile crystals may be found in them. It is also significant that the blue staining granules observed by Tuthill were found only in alcohol-fixed material. Their distribution, however, was not the same as in our material. Tuthill speaks of a universal sprinkling of fine and coarse granules around ganglion and glia cells and of conglomerate masses in the meninges. The masses found in our case were limited to certain areas and were certainly not artefacts, as they could be identified in frozen sections with polarized light, nor do we think that they were in any way related to mucin bodies.

One might, perhaps, assume that being largely adventitial in distribution they represented the end-products of disintegrated nerve cells in process of removal, but for this view there is little support to be found in the histological picture, for it was never possible to find convincing evidence of this substance in neuroglial cells, and its distribution showed no close relationship to the degree of cell destruction. For example, in the optic thalamus, where cell degeneration was marked, only small amounts were present, while the largest quantities were found in the globus pallidus where cell destruction was not particularly evident. A careful study of the appearances in celloidin sections gave the impression that the deposit lay free in the tissues, and although it was certainly not an artefact, it is possible that its localization in the tissues was to some extent determined by the processes incidental to celloidin embedding. No other explanation could account for its presence in small amounts external to the pia and between folia of the cerebellum. It may be, therefore, that prolonged immersion in a mixture of alcohol and ether caused its dislodgment from one position to another.

In their description of extrapyramidal disease affecting particularly the pallidum and pars reticularis of the substantia nigra, Hallervorden and Spatz (1922) refer to deposits of pseudo-calcium in Hortega glia cells, in peri-adventitial spaces and free in the tissues. Material showing very similar properties has been described in a special form of pallido-dentate degeneration by Guillain, Bertrand and Bouques (1936). But although these substances gave a lipoid reaction, most of them could be shown to contain iron, and were therefore of a different nature to the material described above. Through the kindness of Dr. A. Meyer we have been able to examine a peculiar peri-adventitial deposit in the pallidum of a case in which the histological features were largely those of *etât dysmyelinisé*. Just as in our case, it could be stained only after alcohol fixation, but it differed in being soluble in warm 70 per cent. alcohol and was not doubly refractile in polarized light. Fünfgeld (1929) speaks of a peculiar deposit in the lenticular nucleus of a case of status dysmyelinatus, but he gives no details of its chemical nature. It would appear then that in no previous reports has an anisotropic substance having staining reactions identical with those here recorded been described; and it is therefore unfortunate that it was not present in amounts sufficient to permit of its isolation. As already stated, on the basis of the tests for its solubility we believe we were dealing with a lipoid substance showing a close relationship to phrenosin and kerasin.

It is a peculiarity of heredo-degenerative diseases that the pathological process tends to fall specially on certain areas or systems, usually parts of the brain which are phylogenetically recent; and although it would be unwise to lay much stress on the findings in one observation it may be of some significance that the lipoid substance was most abundant in the globus pallidus, the zona reticulata of the substantia nigra and the dentate nucleus of the cerebellum—precisely those regions which are frequently involved in conditions known to be of an heredo-degenerative character.

Relation of the histochemical changes in the nerve cells to those found in the lipoidoses.—Having shown that throughout the nervous system the nerve cells exhibited morphological changes and microchemical reactions similar in every essential feature to those encountered in the juvenile form of family idiocy, it will be profitable to consider this relationship in further detail.

The recent researches of Pick and Bielschowsky (1927) have proved that, remarkable as the ballooning and distortion of the nerve cells is, these features are completely overshadowed in importance by the presence within the nerve cells of an intracellular deposit in all three types of amaurotic idiocy, and that their pathogenesis must be linked with the source of this substance. As is now well known, its presence is considered to be susceptible of only one explanation, namely, that it is the sign of a general disturbance of lipoid metabolism. Thus, amaurotic idiocy, far from being an interesting but isolated form of heredo-degeneration, is in reality only a variant of a general lipoid cellular degeneration of which there are a number of different clinical types.

Of these the most important are Gaucher's disease, Niemann-Pick's disease and Schüller-Christian's disease. With Niemann-Pick's disease amaurotic idiocy has much in common, and it has indeed been claimed that the two diseases are in reality one affection, but with different localization of lipoid storage. On the clinical side it may be recalled that in both there is a strong tendency for a racial incidence, being largely confined to Jews; that in both the condition tends to be familial; to manifest itself in early infancy and to terminate fatally before the third year of life. The evidence of a close relationship between the two diseases has also been furnished by the discovery by Goldstein and Wexler (1931) and others in subjects of Niemann-Pick's disease of the characteristic cherry red spot in the macula, an ophthalmoscopic finding hitherto regarded as pathognomonic of Tay-Sachs' disease. From the pathological standpoint the relationship is even closer. In the hepatosplenomegaly of Niemann-Pick lipoid invasion is almost universal, deposits being found not only in the reticulo-endothelial system, but also in the muscle elements, in glia and in nerve-cells. In the nervous system changes almost identical with those of Tay-Sachs' disease may be found, as Hassin has shown. Though in Niemann-Pick's disease the pathological phenomena are usually less marked, the fundamental type of change is present, the nerve-cell bodies showing the same expansion, an identical accumulation within of lipoid-like substance and microchemical changes in every way similar to those described in amaurotic idiocy. In amaurotic idiocy the visceral organs have not been studied to the same extent as the brain and possibly pathological enlargement of the liver or spleen may have been overlooked. Until recently it was believed that foam cells which are so characteristic of the lipoidoses were not present, but in a recent contribution by Brouwer (1936) reference is made to a typical case of amaurotic idiocy in which Bielschowsky was able to demonstrate their presence in the spleen, thus establishing another link between these two conditions. Not every case, however, of Niemann-Pick's disease exhibits changes in the nervous system. It would appear, therefore, that while the lipoidoses have as an underlying factor common to all a profound disturbance of metabolism, there exist differences in the type of tissue affected. When the disturbance exercises its greatest effects on the nervous system the Tay-Sachs' type is developed; when on the visceral organs Gaucher's splenomegaly appears; and when it involves the entire body the Niemann-Pick or Schüller-Christian types are the result.

Schüller-Christian's disease is characterized histologically by a diffuse collection of lipoid cells, cellular reactions and fibrosis in various organs of the body. In the nervous system the ganglion cells are not extensively involved, nor do they show intracellular deposits. Important changes, however, are found in the white matter. According to Davison (1933), there may be found numerous demyelinated plaques, patchy in distribution and filled with compound granular corpuscles and giant glial cells. In the tuber cinereum extensive fibrosis and gliosis may occur. Foam cells occur in large numbers in the visceral organs of the body, and Chiari (1933) and Davison (1936) have succeeded in detecting their presence in small numbers in degenerated areas of the central nervous system. In Gaucher's type of hepato-splenomegaly, although it is exceptional for the nervous system to be implicated, changes do occur, especially in the juvenile form. In the case of a male infant, reported by Lindau (1930) examination of the markedly enlarged liver and spleen revealed the presence of typical Gaucher cells, while in the nervous system the ganglion cells, especially those of nucleus dentatus, showed morphological changes identical with those found in amaurotic idiocy. The intracellular lipoid inclusion was, however, microchemically inactive.

Nature of the granular deposit in the ganglion cells.—Chemical studies have proved that in this clinical group different lipoids are at fault. According to Epstein and Lorenz (1930), in Gaucher's disease the lipoids are predominantly cerebrosides, chiefly kerasin; in Niemann-Pick's disease the phosphatides are in excess; and in Schüller-Christian's disease cholesterol and its esters predominate. As regards the fourth member of this group, namely Tay-Sachs' disease, chemical analyses have not always yielded consistent results. Weston Hurst (1925), in his study of the lipoids in neuronic degeneration, came to the conclusion that in the juvenile form the abnormal deposit within the nerve cells consists of cerebrosides and phosphatides liberated from chemical combination with some other cellular substance. In a more recent publication Epstein (1931) concludes that in Tay-Sachs' disease we are dealing with a particular form of lipo-phosphatid degeneration.

In our first case the abnormal substance contained within the nerve cells was found to be almost insoluble in acetone, alcohol, chloroform and a mixture of methyl alcohol and chloroform. It was not doubly refractile, and in these properties and in its staining reactions it showed a close, if not identical, resemblance to the granular deposit described by Weston Hurst in a case of cerebromacular degeneration. Its insolubility in chloroform shows that this intracellular substance, if it be of a lipoid nature, exists not in pure form but rather as a compound of lipoid and protein.

CHEMICAL ANALYSES.

The amount of water in the brain of M.—85·6 per cent. in the cortex and 74·4 per cent. in the white matter—was within the limits of the normal, the figures approximating to those reported by Schiff and Stransky (1921) in normal man, and by Ashby and Glynn in the brain of the mental defective.

The total lipoids of the grey matter, 4·34 per cent., and of the white matter, 13·2 per cent., were below the normal, but not markedly so when comparison is made with the figures reported by Ashby and Glynn (1935). When, however, the cerebrosides are considered a very striking departure from the normal is found. Compared with the three controls the figures obtained for the cerebral cortex were very low, being in fact about one-half of the values of the three controls. In the white matter, however, there was no significant reduction in cerebrosides.

How are we to interpret these results?

It is known that cerebrosides show a definite relationship with age, their relative quantity increasing during the first two years of life as myelinization proceeds, while in the later decades the brain suffers a fall in cerebrosides, as, indeed, in all lipoid substances. The age of our patient at death precludes the age factor as a possible influence in determining the diminished cerebroside content, and his mode of dying—sudden collapse after apparent recovery from an attack of bronchitis—does not suggest that the depreciation of lipoid values in the brain could have been a terminal event secondary to some toxic influence, which is also known to influence quantitatively certain of the chemical constituents of the brain.

Of more importance is the question of whether the decrease in the percentage of cortical cerebrosides was related to the profound degree of amentia present, in the sense that chemical changes of this character may be a peculiarity of the idiot's brain. Here it may be said at once that there is no evidence in the literature available to suggest a significant correlation between the mental age of aments and their brain lipoids. A state of complete idiocy is quite compatible with a normal lipoid content in the brain. Tilney and Rosett (1931), for example, found a surprisingly high percentage of lipoids in the brains of two mental defectives, while Ashby and Glynn, utilizing for their study the brains of sixty-two mental defectives and nine normal controls, found no appreciable change in the cerebroside content of the ament's brain. We have already suggested on clinical grounds that this type of osseous dystrophy must be considered a lipoidosis, and we consider that the results of the chemical analyses of the brain of this patient are not inconsistent with this view. As the term lipoidosis connotes, the factor common to all its forms is a disturbance of lipoid metabolism with a storage of various forms of lipoid in the organs and tissues of the body. This piling up of lipoid material may, however, be unevenly distributed, for even in one of the best-known types—Niemann Pick's disease—its distribution is by no means always constant; in some cases the excess of lipoid is confined to extraneural tissues, the brain being apparently normal, while in others there may be histological evidence of lipoid storage in the nervous system as well as in the liver and spleen. Few investigations of a chemical nature appear to have been undertaken; in regard to the brain, in one case of Niemann-Pick's disease Sobotka, Epstein and Lichtenstein (1930) reported an increase of both phosphatides and cerebrosides, and in another investigated by Klenk (1935) the sphingomyelin content was very high and the cerebrosides almost completely absent.

It may be recalled that in our first case the cerebral hemispheres contained many droplets of lipoid substance chiefly confined to the basal ganglia, and that from microchemical tests these were assumed to be composed of cerebrosides. Since they lay free in the tissues, their presence could hardly be looked upon as evidence of lipoid storage, but their obvious relationship to the perivascular spaces did suggest the presence of an abnormal substance undergoing a slow process of removal from the grey matter, and the results of chemical analyses appear to accord with this view.

Our failure to find any reduction of cerebroside in the white matter is of interest, and can perhaps be related to the absence of histological evidence of myelin sheath degeneration.

Clinical considerations.—In addition to the histological manifestations of a generalized disturbance of lipoid metabolism common to this group, it is possible to point to a number of clinical features which are shared by each type. First, it may be noted that though differing widely in their rate of progress and in their degree of menace to life, each of these five diseases, all undoubtedly of congenital origin—Gaucher's disease, Niemann Pick's disease, Schüller-Christian's disease, Tay-Sachs' disease and gargoylism — usually shows a latent period of freedom from symptoms in the early months or years of life during which the subject presents a specious appearance of good health. This is most noticeable in the infantile form of amaurotic idiocy, in which symptoms regularly appear between the third and sixth months.

Secondly, enlargement of the liver and spleen is of great diagnostic significance. Attaining its maximum degree in Gaucher's disease, it also forms an essential part of the picture in Niemann-Pick's disease, and is usually seen in Schüller-Christian's disease and in gargoylism. Only in Tay-Sachs' disease is this enlargement of visceral organs unusual.

Thirdly, evidence of endocrine dyscrasias is not an unusual finding in at least four of the types. In Gaucher's disease (juvenile form), and Niemann-Pick's disease, infantilism has been noted; in Schüller-Christian's disease dwarfism and Fröhlich's syndrome are of frequent occurrence; in Tay-Sachs' disease Velhagen (1932) has recorded the presence of dystrophia adiposo-genitalis, while in gargoylism evidence of endocrine disturbance in the shape ot dwarfism and cretinoid features is almost invariable.

And fourthly, we may note the almost constant presence of osseous lesions and deformities. According to Pick (1933) there is a form of Gaucher's disease that is clinically and anatomically preponderantly osseous, scarcely a bone being spared, but apart from this, lipoid infiltration of the bone-marrow leading to decalcification with resultant gross deformity, and sometime spontaneous fracture, is extremely common. Numerous writers in the past have recorded cases exhibiting kyphosis of the dorsal or upper lumbar spine; and more recently Bloem, Groen and Postma (1936) have called attention to the predilection of the osseous lesions for the lower end of the shaft of the femur. In Niemann-Pick's disease skeletal involvement has been described by Herzenberg (1928). In Schüller-Christian's disease the formation of lipoid deposit in bone is invariably marked by a progressive and extensive decalcification so that large portions of bone may disappear. The geographical skull—the so-called " Landkartenschädel "—which results from calvarial destruction is one of the most constant features. Again, in gargoylism the extremities of the femora and the vertebræ are almost constantly involved, and, although it is not yet proved, it is probable that these changes may be explainable on the basis of lipoid hyperplasia of the bone-marrow.

In the light of the foregoing considerations, it seems difficult to avoid the conclusion that this form of chondro-osteo-dystrophy, gargoylism, is not an isolated disease; but that it belongs to that group of diseases of which a difficulty in metabolizing lipoids is an essential feature, and further, that it possesses in its neuro-pathological aspect a very close relationship to the juvenile form of amaurotic idiocy. There is, however, one important clinical difference. Whereas in amaurotic idiocy, once the disease has become manifest there is, as the title suggests, mental defect of an obvious and progressive type, in gargoylism the degree of intellectual retardation may vary within a wide range. It may either be so slight as to escape recognition, or, as in the former disease, be in the lowest grade, namely idiocy. Whether this variation can be correlated with the histochemical changes in the nerve cells seems more than doubtful, for in our second case, though there was little evidence of an abnormal deposit within in nerve cells, the mental grade of the patient was that of an idiot.

We share the dislike of many workers for eponymous titles, but since the other four diseases in this group have by common usage been designated by the names of those writers who have contributed largely to their elucidation, we consider that at this juncture it would be inadvisable to depart from the practice. We suggest, therefore, in place of the title "Gargoylism" the title "Hurler's disease." Under the generic term "Lipoidoses" there would thus be at least five clinical types—Gaucher's disease, Niemann-Pick's disease, Schüller-Christian's disease, Tay-Sachs' disease and Hurler's disease. To this group there will possibly have to be added Morquio's disease, a form of osteo-chondro-dystrophy which, if not identical with Hurler's disease, bears many points of resemblance to it.

Further pathological considerations.—Before concluding this account, brief references must be made to one or two other features in the pathology of the condition.

In the diagnosis of gargoylism, or Hurler's disease as we prefer to call it, confusion with cretinism seems to be not uncommon, especially in cases seen in the first few years of life. The dwarfism, short neck, heavy expressionless features, obesity and umbilical hernia are common to both conditions, and that this relationship may be more than a casual one is indicated by the histological appearances of the thyroid gland in our two cases. It is true that the activities of this gland are influenced by so many different factors such as age, diet, infection and sexual activity, that the interpretation of the histological picture is by no means easy; but in our two cases in spite of the dissimilarity of the appearances, evidence of gross abnormality was outstanding. In the case of M. the gland had retained its fœtal character, and showed an almost complete absence of colloid. In the second case colloid substance was present, but the secretory cells showed evidence of atrophy with a resultant fibrosis, and it is difficult to escape the conclusion that in both a marked degree of hypothyroidism was present.

The pituitary gland.—In view of the frequency with which enlargement of the sella turcica has been disclosed in radiographic examination of the skull in this condition, the presence of a much enlarged pituitary in our first case is of considerable interest. The enlargement affected both lobes, and microscopic examination failed to disclose any disturbances of the relative proportions of the three types of cell. It is, however, necessary to add that differential cell counts were not attempted. In the second case the gland was not available, but since a photograph of the base of the skull taken by Dr. Brushfield at the post-mortem showed a markedly enlarged sella, it is a fair inference that in this case too the pituitary was much enlarged.

There can be little doubt from these and other cases published that enlargement of the pituitary is a special feature of this disease, but whether this enlargement has any special significance cannot at present be determined. Possibly we are here dealing with a form of so-called thyropituitarism, and in this connection one may recall that in one of their cases Ellis and his co-workers noted a facial suggestion of infantile acromegaly. If, as Raab (1928) has claimed, lipoid metabolism is controlled by a pituitary-hypothalamic mechanism—and the pathological findings in Niemann-Pick's disease certainly support this view—the enlargement of the gland and the gliosis found in the grey matter bordering on the wall of the 3rd ventricle must be given a special significance.

Hydrocephalus.—Yet another cranial abnormality which occurs with some degree of frequency in this condition is hydrocephalus. In the case of M., though the cranium was not enlarged, a condition of unilateral internal hydrocephalus was disclosed; in the second case there was no ventricular distension. Unilateral hydrocephalus is uncommon, and in the majority of recorded cases degenerative changes have been present in the surrounding brain substance. These have usually been either a chronic leptomeningitis, an encephalitis, or vascular disease, and, given one of these three conditions, it is obvious that even without increased intraventricular pressure the softened brain substance may gradually yield before the cerebrospinal fluid which it imprisons, the process being rather analogous to the aneurysmal dilatation of a blood-vessel whose wall is defective. Such an explanation, though adequate for those cases in which the enlargement is limited to one part of a ventricle, fails to afford a satisfactory explanation for the condition in which, as in this case, the whole cavity is uniformly dilated; and, where such exists, it is necessary to fall back on the assumption that lessened resistance of the wall of the hemisphere extends over a far wider area than the local cortical lesion would suggest. But, whatever may be the explanation, when viewed in the light of the clinical findings there is little doubt that the dilatation must have been of long standing for weakness of the right arm had been present from an early age.

The liver and spleen.—Another important peculiarity in this case is the absence of any evidence of the enlargement of liver and spleen, either in childhood or in the last years of his life. The liver was not, however, normal, as it showed a marked decrease in the bulk of its left lobe along with thickening of the capsule; and it is possible that these findings represented a shrinkage consecutive to a former enlargement, in which there had been lipoid storage. Through an unfortunate oversight, no pieces of either organ were retained for histological study, but in the second case the liver was of normal weight and the section which we were able to obtain from the Fountain Hospital showed no striking departure from the normal. In particular, no foam cells were present either in this or in any of the other organs studied, so that apart from the findings in the ectodermal system of a substance of probably lipoid nature these two cases provide no evidence of abnormal lipoid storage within the body. Nevertheless, when it is remembered that the taxonomic position of Tay-Sachs' disease has only recently been established by the discovery of histochemical changes in the spleen, it would be rash to assume that future studies of mesodermal tissues will not provide histological proof for the inclusion of this form of chondro-osteo-dystrophy within the group of diseases which constitute the lipoidoses.

SUMMARY AND CONCLUSIONS.

Two cases of the form of chondro-osteo-dystrophy termed gargoylism are here reported. In one of them a comprehensive study of the central nervous system was made, in the other a limited examination. Both cases were atypical in that enlargement of the liver and spleen was not detected during life nor found at autopsy. In both marked enlargement of the pituitary gland was present, and, in one, microscopic examination showed that this enlargement was due to a general cellular hyperplasia. Both thyroid glands were definitely abnormal, and the histological appearances, though dissimilar, suggested diminished secretion. No evidence of lipoid storage in the reticulo-endothelial system was found. A section of the liver of the second case showed neither foam cells nor marked pathological changes. In both cases, in every part of the nervous system examined the ganglion cells showed a striking alteration, the cytoplasm being distended by the deposit of an abnormal substance, the Nissl granules reduced in number and crowded to one portion of the cell, the nucleus dislocated to one side, and the cell processes but little affected. These changes were much less evident in the second case. The lipoid material was extremely resistive to solvents, and was not doubly refractile. In addition to the intracellular deposit, masses of lipoid substance giving different staining reactions and different behaviour to solvents were discovered lying free in the basal ganglia and in certain other situations. The substance was believed to be composed of cerebrosides.

The myelin sheaths and axis cylinders were almost intact and fibrillary glial reaction was most marked in the optic thalamus and the paraventricular portion of the hypothalamus. The mesodermal elements were relatively little affected and lipoid storage cells were not found in them.

Chemical analysis of the brain in Case 1 showed a marked reduction of cerebrosides in the cerebral cortex but not in the white matter.

In Case 1 a unilateral hydrocephalus was present, and in both cases the cerebellum was a little small in proportion to the size of the cerebrum.

Except in a few minor details the histological findings in the nervous system were similar to those described by Tuthill in another case of this form of chondro-osteo-dystrophy; they support fully his claim that the appearances resemble in the closest degree those found in the juvenile form of amaurotic idiocy. The view is expressed that, notwithstanding the failure to find histological evidence of derangement of lipoid metabolism outside the nervous system, this condition must be accepted as a manifestation of such a pathological process and consequently belongs to the group of lipoidoses.

As eponymic designations have been accepted for the recognized principal types in this group, we would comply with common usage by suggesting the term Hurler's disease for this form of chondro-osteo-dystrophy.

We have to thank Dr. R. W. B. Ellis for giving information which led to our being able to secure the history and pathological material of our second case, and to express our indebtedness to Dr. Jacobson from whom they were obtained. Our thanks are also due to Dr. Meyer for the loan of slides containing abnormal chemical deposits and for his helpful interest in the findings.

PLATE V.

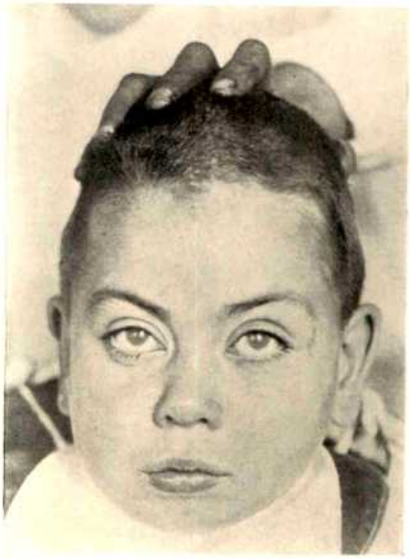


FIG. 1.

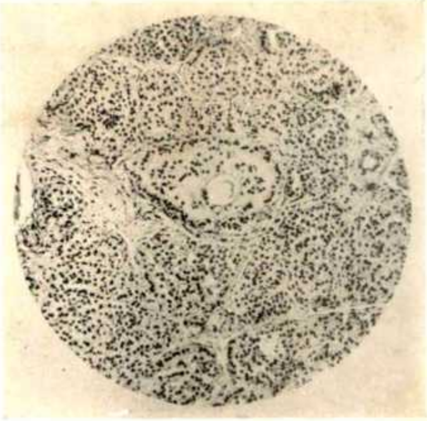
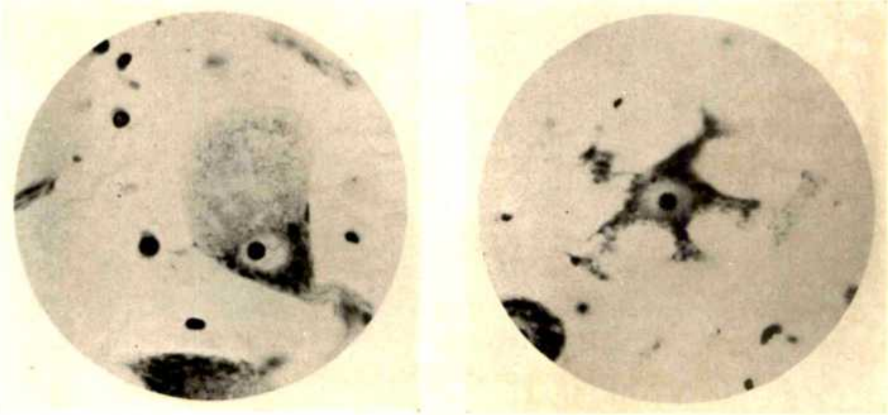


FIG. 2.



A.

B.

FIG. 3.

To illustrate paper by W. R. Ashby, R. M. Stewart and J. H. Watkin.

PLATE VI.

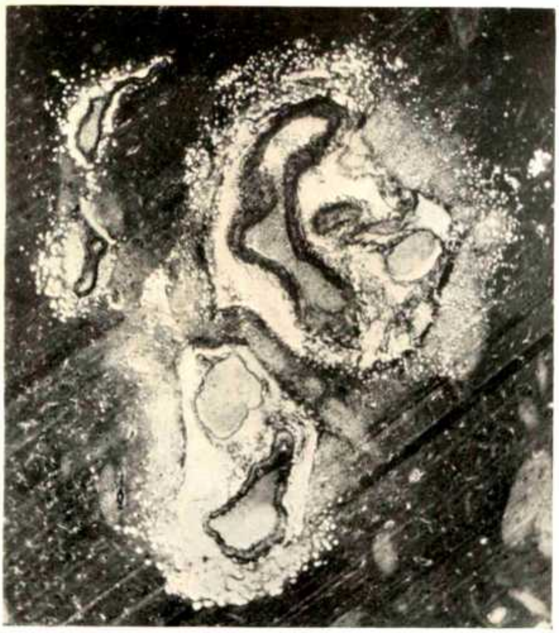
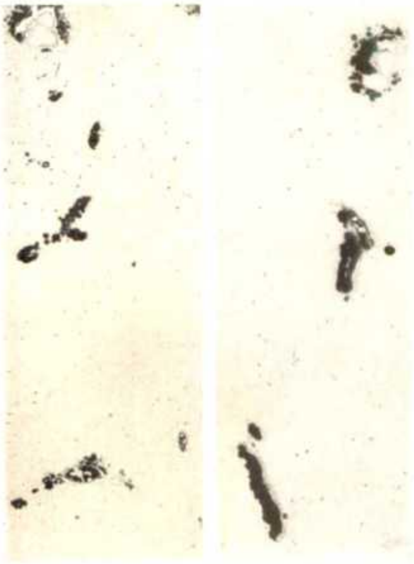


FIG. 4.



A. B.

FIG. 5.

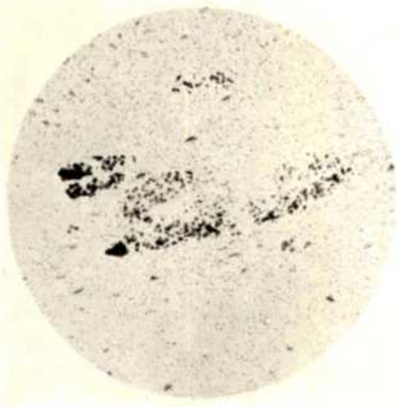


FIG. 6.

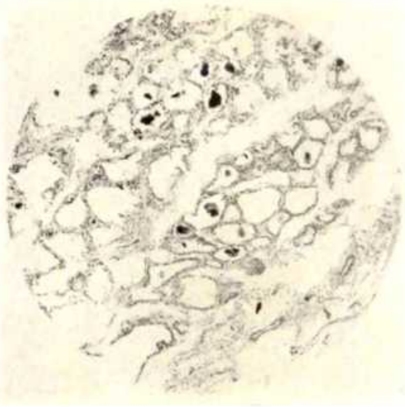


FIG. 7.

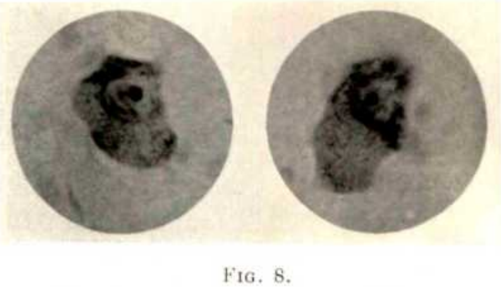


FIG. 8.

To illustrate paper by W. R. Ashby, R. M. Stewart and J. H. Watkin

REFERENCES.

Ashby, W. R., and Glynn, A. *Journ. Neurol. and Psychiat.*, 1935, **16**, 193.
Bloem, T. F., Groen, S., and Postma, C. *Quart. Journ. Med.*, 1936, **5**, 517.
Brouwer, B. *Proc. Roy. Soc. Med.*, Lond., 1936, **29**, 579.
Buscaino, V. *Riv. de patol. nerv.*, 1920, **25**, 197.
Chiari, H. *Virchow's Arch. f. path. Anat.*, 1933, **288**, 527.
Davis, D. B., and Currier, F. P. *Journ. Amer. Med. Assoc.*, 1934, **102**, 2173.
Davison, C. *Arch. Neurol. and Psychiat.*, 1933, **30**, 75.
Idem. Ibid., 1936, **35**, 629.
Ellis, R. W. B., Sheldon, W., and Capon, N. B. *Quart. Journ. Med.*, 1936, **5**, 119.
Epstein, E., and Lorenz, K. *Hoppe-Seyl Zeit.*, 1930, **192**, 145.
Epstein, E. *Rev. Neurol.*, 1931, **11**, 524.
Fünfgeld, F. *Journ. f. Psych. u. Neurol.*, 1929, **40**, 85.
Goldstein, I., and Wexler, D. *Arch. Ophthal. N.Y.*, 1931, **5**, 704.
Grynfeltt, E. *C.R. Soc. Biol.*, Paris, 1923, **89**, 1264.
Guillain, G., Bertrand, I., and Bouques, L. *Rev. Neurol.*, 1936, **65**, 921.
Hallervorden, J., and Spatz, H. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1922, **79**, 41.
Hassin, G. B. *Arch. Neurol. and Psychiat.*, 1924, **12**, 640.
Idem. Ibid., 1930, **24**, 61.
Herzenberg. *Virchow's Arch.*, 1928, **269**, 614.
Hiroisi, S., and Lee, C. C. *Arch. Neurol. and Psychiat.*, 1936, **35**, 827.
Hurler, G. *Zeitschr. f. Kinderheilk.*, 1919, **34**, 220.
Hurst, Weston. *Brain*, 1925, **48**, 1.
Jewesbury, R. C., and Spence, J. C. *Proc. Roy. Soc. Med.*, Lond., 1921, **14**, 27.
Klenk, E. *Hoppe-Seyl. Zeit.*, 1935, **235**, 24.
Lhermitte, J. *Arch. Neurol. and Psychiat.*, 1924, **12**, 620.
Lindau, A. *Acta Psychiat.*, 1930, **5**, 167.
Morquio, L. *Arch. de Med. des Enf.*, 1929, **32**, 129.
Nonne, M. *Deutsch. Zeitschr. f. Nervenheilk.*, 1924, **83**, 263.
Pick, L., and Bielschowsky, M. *Berl. klin. Wchnschr.*, 1927, **34**, 1631.
Pick, L. *Amer. Journ. Med. Sci.*, 1933, **185**, 453.
Raab. *Zeit. f. d. ges. exper. Med.*, 1928, **62**, 366.
Schiff, E., and Stransky, E. *Jahr. f. Kinderheilk*, 1921, **96**, 245.
Sobotka, Epstein, E. L., and Lichtenstein. *Arch. Path.*, 1930, **10**, 677.
Spielmeyer, W. *Nissl's Arb.*, 1908, **2**, 193.
Tilney, F., and Rosett, J. *Bull. Neurol. Inst., N.Y.*, 1931, **1**, 23.
Tuthill, C. R. *Arch. Neurol. and Psychiat.*, 1934, **32**, 198.
Velhagen, K., jun. *Klin. Monatsbl. f. Augenheilk.*, 1932, **89**, 1.
Vogt, H. *Monatschr. f. Psychiat. u. Neurol.*, 1907, **22**, 403.

EXPLANATION OF PLATES.

Plate V.

Fig. 1.—*Case* 1. Patient, S. M., when 8 years of age. Photograph by Dr. Brushfield.

Fig. 2.—Section of thyroid gland, for the most part consisting of solid masses of cells; one acinus near the centre of the figure contains colloid. Hæmatoxylin-eosin. × 96.

Fig. 3.—Morbid nerve cells showing various degrees of ballooning. A and B, cervical cord; anterior horn. Thionin. × 600.

Plate VI.

Fig. 4.—Drawing showing lipoid deposit aggregated round vessels in globus pallidus. Aniline blue, orange G and neutral red. × 56.

Fig. 5.—Lipoid deposits in neighbourhood of vessels: A, putamen; B, globus pallidus. Thionin. × 25.

Fig. 6.—Small masses of lipoid in dentate nucleus of cerebellum. Thionin. × 63.

Fig. 7.—*Case* 2. Section of thyroid showing parenchymatous atrophy. Hæmatoxylin eosin. × 64.

Fig. 8.—*Case* 2. Nerve cells of optic thalamus, showing ballooning and granular inclusion. Unna-Pappenheim. × 600.

TOXIC HYDROCEPHALUS.

BY DOUGLAS McALPINE.

(From the Department of Nervous Diseases, Middlesex Hospital.)

FROM time to time cases are met with in children and young adults in which symptoms of increased intracranial pressure develop rapidly. In some of these cases the examination of the nervous system is singularly negative apart from papillœdema and an ocular palsy. The co-existence of an otitis media may clarify the position, but in other cases the cause may not be obvious and the possibility of a tumour of the posterior fossa has to be carefully considered. The purpose of the present paper is to describe a small number of cases in which an external hydrocephalus was present, and in which there was good reason to believe an infection, other than an otitis media, was the cause of the condition. Such cases have been recognized from the end of the last century under such names as "serous meningitis" and "pseudo-tumours." Quincke [6] first used the term "serous meningitis" to include a heterogeneous collection of cases, some of which appear to belong to the group which concerns us now, but at least one case was obviously an example of spontaneous subarachnoid hæmorrhage. It was not until 1912 that two papers appeared which clarified the position.

Passot [5], in a thesis, distinguished between non-purulent and purulent intracranial complications of otitis media by an examination of the cerebrospinal fluid. He described cases in which there were symptoms of increased intracranial pressure alone. The cerebrospinal fluid pressure was raised, but it contained neither an increase in the number of cells, nor in the amount of protein. He came to the conclusion that this condition was probably due to an excess of cerebrospinal fluid in the subarachnoid space, rather than in the ventricles (hydropisie méningée). Warrington [9], a few months later, in a paper entitled "Intracranial Serous Effusion of Inflammatory Origin," recorded four cases. He believed that the progress of an inflammatory effusion within the skull may be arrested at the serous stage. "The primary cause is commonly a near or distant focus of septic infection. The toxins formed by this, but not the micro-organism, stimulate the vessels of the meninges, brain, or ependyma and choroid plexus, to the formation of excessive fluid." Symonds [8] in 1931, revived interest in this subject in a paper entitled "Otitic Hydrocephalus." He reviewed the literature of serous meningitis, referring particularly to the work of Passot, and he described three cases of his own associated with otitis media. He emphasized the main features of the clinical picture, namely advanced papillœdema in association with a general state of physical fitness, an alert mind, the absence of any localized signs, and a normal spinal fluid apart from a greatly increased pressure. The present writer shares Symonds's view on the unsuitability of the term "serous meningitis" in describing these cases. However, the adjective "otitic" adopted by Symonds to describe this type of hydrocephalus appears to have too special an implication. The term "toxic" is therefore suggested to describe the hydrocephalus which may follow, not only otitis media, but also nasopharyngeal and other sources of infection.

The following are reports of five cases in which nasopharyngeal infection seemed to be the causal factor:—

Case 1.—*Female, aged* 14. *July,* 1934, *sore throat and stiff neck followed by failing vision, diplopia, headache and papillœdema. Repeated lumbar puncture: subsidence of papillœdema and improvement in vision.*

E. L., Reg. No. 69026. Was admitted to the Neurological Ward, Middlesex Hospital, on December 15, 1934.

History.—The patient had been in normal health until July, 1934, when she developed a sore throat accompanied by a rash on the face, arms and legs. These symptoms gradually cleared up, but two weeks later they returned, and during part of this time she complained of a stiff neck, and the head was slightly drawn over to the right. Towards the end of September her mother noticed that she was holding her book close to the eyes when reading. At the end of November she had a severe "cold" in the head. This was followed by a return of the stiff neck, now accompanied by headache. On December 1 she complained of double vision on looking to the left. There was no vomiting. Mr. Maurice Whiting saw her on December 14 and noted that the vision was, right $\frac{6}{24}$, left $\frac{6}{36}$. There was bilateral papillœdema. The visual fields showed an atypical right homonymous hemianopia.

Examination.—She was admitted to the Neurological Ward on the following day. Temperature 98° F., pulse 100, respirations 20 per minute. Weight 12 st. 2 lb. The face was rounded. There was a considerable generalized increase of fat; the secondary sexual characteristics were normally developed. She complained of frontal headache. Cerebration seemed slowed, but she did not appear ill. The pupils were under the effect of atropine. There were approximately six diopters of papillœdema with exudate in both macular regions. There was complete paresis of the left external rectus. There was no facial weakness, and no deafness, and the remaining cranial nerves were normal. Suboccipital tenderness was not found. Tone, power, reflexes and co-ordination were normal in the upper and lower limbs, and the gait was normal. The heart sounds were normal. Blood-pressure 116/60. There was no aural or nasal discharge. The fauces were injected. There was no polyuria. A lumbar puncture showed cerebrospinal fluid pressure of over 300. Cerebrospinal fluid contained 3 cells per c.mm.; protein 0·025 per cent.; Lange curve normal; Wassermann reaction negative. The headache disappeared after this lumbar puncture. She was transferred to the Hospital for Epilepsy and Paralysis, Maida Vale, for further observation.

She remained free from headache. Five lumbar punctures were performed during the next three weeks. Vision began to improve and the papillœdema slowly subsided. Diplopia disappeared at the beginning of January, 1935. The visual fields were at first generally constricted, left more than right, with a tendency, however, to flattening both above and below. Subsequently they became fuller. On January 2, 1935, Mr. T. C. Summers noted a bi-nasal defect in the lower quadrants with a 2/2000 object.

January 16, 1935: There were two diopters of papillœdema. Vision $\frac{6}{18}$ both eyes. There were signs of early post-neuritic atrophy.

February 3: The discs were now flat. The vision was $\frac{6}{9}$ (partial) both eyes.

February 7: The cerebrospinal fluid pressure was 145 mm. of water. The patient has since remained well and free from headaches. When seen on May 1, 1937, there was a moderate degree of post-neuritic atrophy. Vision was right $\frac{6}{12}$, left $\frac{6}{9}$ (partial). Menstruation was normal.

Case 2.—*Female, aged* 18. *October*, 1934, *complained of headache. One month later high-grade papillœdema without localizing signs. No definite nasopharyngeal infection. Repeated lumbar punctures were followed by disappearance of headache and slow subsidence of papillœdema. March*, 1935, *headache reappeared following a "cold"; mild papillœdema still present. March*, 1937, *discs flat, vision full.*

M. B., Reg. No. 68353. Was admitted to the Middlesex Hospital on November 27, 1934.

History.—This young married woman had been working in a factory matching wall-papers when, at the end of October, 1934, she began to suffer from dull frontal headaches. A week later, after washing her hair, she experienced severe pain at the back of the neck which radiated to the shoulders and down both arms. These pains were intermittent, but were especially noticeable in the morning and were aggravated by movement. About the middle of November she experienced pain around the eyes and nose and to a slight degree in the left ear. No history of nasal catarrh, sore throat or aural discharge could be obtained. The headache and occipital pain had subsided considerably by the time she was admitted to Hospital at the end of

November. She appeared to be a healthy young woman weighing 10 st. 2 lb.

Examination. — Temperature 98·6° F. She showed approximately 5 diopters of papillœdema each eye; a few hæmorrhages were present around the right disc; vision was $\frac{6}{6}$ in both eyes. The visual fields were full. The pupils were moderately dilated and reacted normally, ocular movements were full and there was no diplopia or nystagmus. There was no facial weakness or deafness. The remaining cranial nerves were normal. There was no abnormal posture of the head; movements of the head were free; suboccipital tenderness could not be elicited. Routine examination of the central nervous system on several occasions was completely negative, apart from depression of the upper limb reflexes. Examination in the Ear, Nose and Throat Department was completely negative, except for retracted drums and a mild pharyngitis. The heart was normal; blood-pressure was 120/75. On November 28, 1934, lumbar puncture showed a cerebrospinal fluid pressure of well over 300 mm. of water; 15 c.c. were withdrawn slowly. The headache was much relieved within a few hours. The fluid contained 2 cells per c.mm.; the total protein was 0·03 per cent.; Lange colloidal gold curve was normal, and the Wassermann reaction was negative.

Magnesium sulphate was given each day by the mouth. Lumbar puncture was repeated on December 8. The pressure was 260 mm.; 15 c.c. were withdrawn and the final pressure was 185 mm. On December 12 cerebrospinal fluid pressure was 170 mm.; 8 c.c. were withdrawn and the final pressure was 100 c.c. The patient was now entirely free from headache and the papillœdema began to subside. She remained free from headache, but 2 diopters of papillœdema were still present in March, 1935, when she contracted a severe "cold." Mr. C. P. Wilson reported that all the sinuses were clear.

She was readmitted on March 15, 1935. Lumbar puncture showed a cerebrospinal fluid pressure of 190, but on March 28 it had risen to 240 mm. and this figure was again recorded four days later. As the patient was unwilling to undergo further puncture, she was allowed to go home. On June 19 the vision was $\frac{6}{6}$ both eyes. The right fundus was normal, but there was minimal papillœdema on the left side (Mr. Affleck Greeves). On March 16, 1937, she reported herself as fit and working hard. She had continued free from headache, except when worried. Both discs were quite flat and of a good colour, but the edges of the left disc were still indistinct. Vision $\frac{6}{6}$ both eyes.

Case 3.—*Male, aged* 11. *April,* 1936, "*cold,*" *frontal headache, external rectus palsy, papillœdema and impairment of vision. Rapid improvement after lumbar puncture. Antrum infected. Subsequently signs of Hodgkin's disease developed. March,* 1937, *streptococcal otitis media occurred.*

F. M., Reg. No. 92858. Admitted to Neurological Ward, Middlesex Hospital, May 13, 1936.

History.—This was obtained both from the patient, who was intelligent, and from his father. During the first week of April, 1936, this boy complained of severe pain at the back of both eyes, and at the same time he had a "cold." The nose was "stuffed up," but there seemed to be no actual discharge. The throat was not sore, and he had no earache. The pain continued until the middle of April, when the headache disappeared, but about this time he saw double, and this persisted up to the time of his admission to Hospital on May 13.

About May 3 he had a stomach-ache, and vomited once. His father stated that after the first fortnight he had seemed quite well and had been full of fun, playing about the house. No failure of vision had been noted by the patient. There was no history of aural discharge.

Examination.—Temperature 99·8° F., pulse 108, respiration 20. The patient was mentally alert. The visual fields were full to a 1 mm. object. Vision left eye $\frac{6}{18}$, right eye $\frac{6}{12}$. About 2 diopters of papillœdema were present in each eye. There were several hæmorrhages around each disc. Both pupils reacted sluggishly to light. There was no detectable ocular paresis, but diplopia was present on looking to either side and downwards. There was no nystagmus and no facial weakness or deafness. The remaining cranial nerves were normal. There was no alteration in tone, power, reflexes, sensation, or co-ordination in the upper and lower limbs, except that the upper limb reflexes were depressed. Gait was normal. The heart was normal. Blood-pressure 118/65. There was no aural or nasal discharge; the tonsils were moderately enlarged. A small enlarged gland was felt in the left side of the neck. The liver and spleen were not enlarged and nothing abnormal was noted in the examination of the abdomen.

May 15, 1936: A lumbar puncture showed the pressure of the cerebrospinal fluid to be over 300 mm. of water; 15 c.c. were removed slowly. The final pressure was 100 mm. The cerebrospinal fluid contained 13 lymphocytes; 105 red cells; protein 0·025 per cent.; Lange curve normal; Wassermann reaction negative.

May 17: The patient no longer complained of double vision. Cerebrospinal fluid pressure was now 120 mm. of water; 3 c.c. were withdrawn.

May 18: Vision was now $\frac{6}{6}$ both eyes.

May 22: An X-ray of nasal sinuses showed slight thickening of the lining membrane of the right antrum, and to a lesser extent of the left antrum. Mr. C. P. Wilson reported as follows: "No obvious nasal discharge. Antra do not illuminate quite normally. I think there has been a definite sinusitis which is clearing up and is now practically well."

May 25: Papillœdema had further subsided. The cerebrospinal fluid pressure was 160 mm. of water. He was discharged on June 3. There was no measurable papillœdema and the vision was $\frac{6}{6}$ in both eyes.

At the end of June a painless swelling appeared above the left clavicle. He was later admitted to a sanatorium where the condition was considered to be non-tuberculous. He was readmitted to the Middlesex Hospital on

February 22, 1937. A large, firm, glandular swelling was present in the posterior triangle of the left side of the neck; a few shotty glands were felt in both inguinal regions. Several large masses were felt in the right side of the abdomen. The edge of the liver could not be felt, but the spleen was moderately enlarged. A blood-count showed a count of 13,000 white cells, of which 9 per cent. were eosinophils. A diagnosis of Hodgkin's disease was made which was confirmed by the histological appearance of a portion of the gland removed from the neck. On March 4 he developed an acute otitis media from which a hæmolytic streptococcus was grown in large numbers. There were no signs of a return of the hydrocephalus. The discs were normal and the vision was $\frac{6}{6}$. He was transferred to the care of Dr. C. E. Lakin, who confirmed the diagnosis of Hodgkin's disease, but was of the opinion that there was a secondary tubercular infection of the abdominal glands.

Case 4.—*Male, aged* 16. *July,* 1936, *during recovery from concussion, developed sore throat, severe headache, external rectus palsy and papillœdema. Ventriculogram normal. Lumbar puncture, with subsidence of papillœdema and recovery with $\frac{6}{9}$ vision. Tonsillectomy.*

E. W., Reg. No. 94867. Was admitted to Middlesex Hospital on July 10, 1936, under Mr. Sampson Handley.

History.—On that date he fell off a van and was unconscious for a short time. He was conscious when admitted, and there was no bleeding from the nose or ears. He was found to have a fracture of the left clavicle. No focal signs were present in the central nervous system. An X-ray of the skull was negative. He vomited twice during the first twelve hours after admission. He was lumbar punctured on July 14; the fluid was normal. During the next fortnight he complained of severe frontal headaches and he vomited on more than one occasion. During the second week in hospital he complained of double vision on looking to the right.

Examination.—I saw him for the first time on July 30. He complained of headache. He was mentally alert. Examination of the central nervous system was negative, apart from slight paresis of the right external rectus, fine lateral nystagmus and approximately two diopters of papillœdema with recent hæmorrhages around each disc. He was transferred to the Hospital for Epilepsy and Paralysis, Maida Vale, as a suspect posterior fossa tumour. During my absence on holiday, Dr. S. Nevin took charge of the case.

August 4, 1936: Vision right $\frac{6}{18}$, left $\frac{6}{9}$. Visual fields showed a generalized constriction. There was slight paresis of the right external rectus with diplopia. There was fine rapid nystagmus on looking to the right, and coarser movements to the left. Corneal reflexes were brisk, there was no sensory loss on the face. There was no facial weakness and no deafness, and the remaining cranial nerves were normal. Apart from a depression of the deep reflexes in the upper limbs, the rest of the examination of the central nervous system was negative. On August 5 he developed a catarrhal rhinitis. During the next two weeks he continued to complain of headache and vomited several times.

August 11 : Cerebrospinal fluid pressure was 280 mm. of water. The fluid contained 4 cells per c.mm. ; protein 0·01 per cent. ; Lange curve normal ; Wassermann reaction negative.

August 20 : Mr. G. H. MacNab carried out a ventriculogram. The pictures were normal (fig. 1). The headaches were relieved. On September 25 he no longer complained of headaches. The papillœdema had definitely subsided and the hæmorrhages had been absorbed. Ocular movements were full and there was no nystagmus. A history of a sore throat during his stay in the Middlesex Hospital was obtained, and of an attack of acute nephritis one year previously. The right tonsil was much enlarged, and appeared ulcerated. A diagnosis of serous meningitis was made and tonsillectomy was advised.

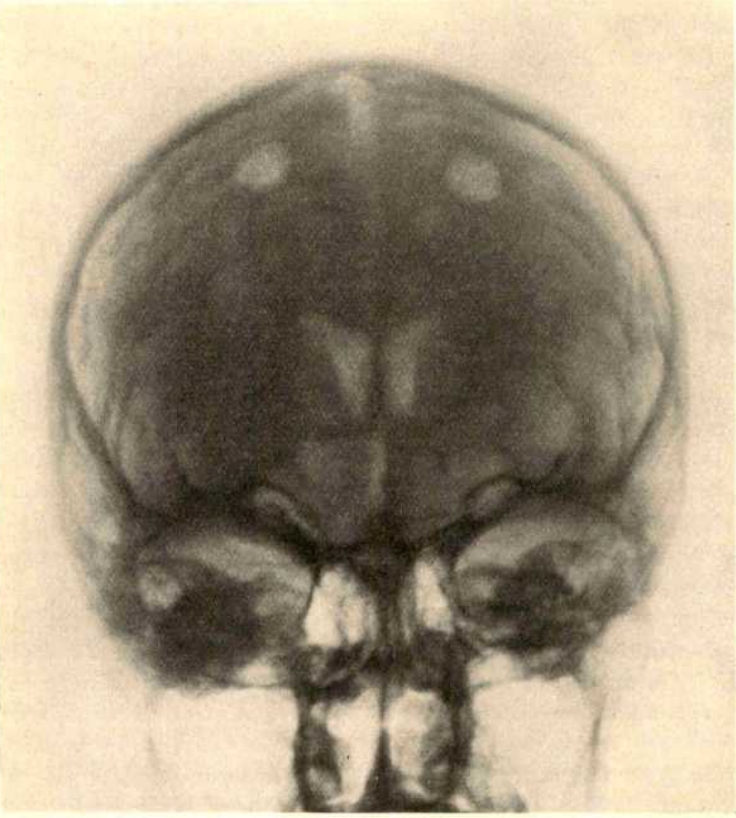


FIG. 1.—*Case* 4. Toxic hydrocephalus. Ventriculogram. Normal anterior horns.

September 29 : Cerebrospinal fluid pressure was 230 mm. of water. 10 c.c. was withdrawn slowly, the final pressure being 120 mm. of water. The papillœdema continued to subside, so that at the beginning of October it was not measurable. A fresh tonsillitis and rhinitis delayed the tonsillectomy until October 29.

November 10: Vision right $\frac{6}{6}$, left $\frac{6}{6}$. Cerebrospinal fluid pressure 110 mm. of water. 5 c.c. were removed. Final pressure 95 mm. of water. He was discharged to a convalescent home at the end of November apparently well. He returned to work in January, 1937. The patient has remained free from headache. When last seen on May 20, 1937, vision was $\frac{6}{6}$ both. The discs were quite flat and of good colour. An examination of the central nervous system was entirely negative.

Case 5.—Female, aged 11. *November,* 1936, *headache, vomiting and papillœdema, with impairment of vision and doubtful dilatation of lateral ventricles. Repeated lumbar punctures, gradual subsidence of the papillœdema and return of vision. February,* 1937, *relapse following tonsillitis. Tonsillectomy and repeated lumbar punctures. Slow subsidence of papillœdema. Normal vision.*

E. A., Reg. No. A. 1435. Admitted to the Neurological Ward, Middlesex Hospital, December 5, 1936.

History.—According to her mother the child was in good health until November 2, 1936, when she vomited, and at the same time complained of headache referred to the left frontal region and behind the eyes; it was especially marked in the mornings. These symptoms increased in severity. On November 22 she complained of a mist in front of her eyes and on the following day she saw double. About this date she appeared rather drowsy and did not want to leave her bed. From approximately November 27 the vomiting ceased and the headache diminished and had disappeared by the beginning of December. She was seen by Dr. H. L. Marriott at the Miller Hospital, Greenwich, who found papillœdema and referred her to me. No history of aural or nasal discharge, tonsillitis, boils, or any focus of infection prior to the onset of the illness could be elicited.

Examination.—On admission to the Middlesex Hospital on December 5, 1936, temperature 98° F., pulse 76, respirations 20. She was a well-nourished child with a rounded face and a slight general increase of subcutaneous fat. She did not appear ill and was not suffering from headache. She was mentally very alert and quick in carrying out various tests during the examination. Ophthalmoscopic examination showed approximately four diopters of swelling of both discs. There were two small hæmorrhages below the right disc. The vision was $\frac{6}{18}$ (partial) both eyes. The visual fields were full to a 2 mm. white object. There was slight convergent strabismus of the left eye, due to weakness of the left external rectus. The pupils were dilated and reacted somewhat sluggishly to light. Slow nystagmus was present on looking to the right. Sensation on the face was normal, as were the facial movements. Hearing was not diminished and there was no discharge from the ears. The remaining cranial nerves were normal. There was no abnormal posture of the head, and suboccipital tenderness was not elicited. The arms showed a slight degree of hypotonia. Power appeared normal, and there were no signs of disturbance of cerebellar function. The arm reflexes were obtained with difficulty. The abdominal reflexes were brisk and equal. The lower limb reflexes were brisk and the plantar responses flexor. The gait was normal.

The apparent well-being of this child, the absence of headache, despite well-marked papillœdema, suggested that the condition might be one of toxic hydrocephalus, rather than posterior fossa tumour. It was considered necessary to tap the ventricles before carrying out lumbar puncture, in order to establish whether the hydrocephalus was of the internal or external variety. This was done by Mr. P. B. Ascroft on December 12, 1936. He found the ventricles to be slightly dilated, but the pressure was not much raised. 20 c.c. of cerebrospinal fluid were withdrawn. Attempts to inject air were unsuccessful.

December 16, 1936: The patient did not complain of headache. Cerebrospinal fluid pressure was not estimated, but did not appear much increased. 8 c.c. of fluid were withdrawn. It contained 2 cells per c.mm.; protein 0·03 per cent.; Wassermann reaction was negative.

December 20: The papillœdema appeared to be definitely subsiding and now measured approximately two diopters. There was no nystagmus. The cerebrospinal fluid pressure was 190 mm. of water. 8 c.c. were withdrawn, the final pressure being 110 mm. of water.

December 29: The cerebrospinal fluid pressure was 140 mm. of water. This lumbar puncture was followed by headache and vomiting during the next few days.

January 4, 1937: Slight headache was still present. Papillœdema now measured one diopter on the right and less than this on the left. Vision, right $\frac{6}{6}$, left $\frac{6}{6}$. There was now no nystagmus and double vision could no longer be elicited.

January 12: Both optic discs were now quite flat and the patient was free from symptoms. Re-examination of the central nervous system was negative. In view of enlarged and unhealthy tonsils it was decided to have tonsillectomy performed at an early date. She was discharged and asked to attend weekly.

January 26: She appeared perfectly well. The vision was now $\frac{6}{5}$ both eyes, and the discs were quite flat and well coloured.

February 9: Her mother stated that a week previously she had had a "cold" in the head and sore throat, and at the same time complained of frontal headache. Both discs now showed approximately one diopter of papillœdema with marked fullness of the veins. The right vision was $\frac{6}{6}$, the left $\frac{6}{6}$ (partial). There was no nystagmus and no diplopia. The fauces and tonsils were reddened and congested. The rest of the examination was negative. She was readmitted the same day. Temperature 98·4°F., pulse 80, respirations 20.

February 10: The cerebrospinal fluid pressure was over 300 mm. of water. 30 c.c. were withdrawn and the final pressure was 150 mm. of water. A Dick test was strongly positive. A swab from the throat was negative for hæmolytic streptococci.

February 12: The cerebrospinal fluid pressure was well over 300. 37 c.c. were withdrawn and the final pressure was 150 mm. of water.

February 17: Three diopters of papillœdema were now present. Vision, right $\frac{6}{6}$, left $\frac{6}{6}$. It was thought advisable to have a tonsillectomy done at once and this was carried out on this date. Just before operation cerebrospinal fluid pressure still over 300 mm. of water; 35 c.c. were withdrawn. Final pressure was 145 mm. of water.

February 19: Cerebrospinal fluid pressure was 240 mm. of water. 10 c.c. were removed and the final pressure was 140 mm. of water. The patient remained free from headache.

February 22: Papillœdema was slightly less marked and re-examination of the central nervous system was negative. The cerebrospinal fluid pressure remained over 300 mm. of water; 27 c.c. were removed. The final pressure being 145 mm. of water.

February 23: Slight headache was complained of and in view of this it was decided to discontinue lumbar puncture for the present.

February 26: "Papillœdema has considerably subsided; approximately 1·5 diopters in each eye" (Mr. R. Affleck Greeves). The patient appeared well.

March 5: Cerebrospinal fluid pressure was 220 mm. of water; 15 c.c. were withdrawn. The final pressure was 110 mm. of water.

She was discharged from hospital on April 27. When seen again on May 18 she was free from headache and appeared well. "Right disc edge still slightly blurred, but swelling not measurable. Left disc practically normal" (Mr. R. Affleck Greeves). Vision was $\frac{6}{6}$ both eyes.

CLINICAL FEATURES.

Age of incidence.—The ages of the five patients reported in this paper ranged between 11 and 18 years. This age incidence agrees with the findings of Symonds that the condition is rarely met with apart from childhood and adolescence. The reason for this must remain at the present time problematical, but presumably it may depend on a greater sensitivity of the choroid plexus to the effect of toxins in the young as compared with adults.

Precipitating factors.—In none of the cases was there a history of otitis media, nor was any evidence of this condition found when the patients came under observation. In Case 2 pain was felt in the left ear during the acute phase, but the ear-drum appeared normal three weeks later. In two cases a "sore-throat," and in another two a "cold," preceded the onset of headache. An exacerbation of the hydrocephalic symptoms following a fresh "cold" occurred in three cases, being particularly clear in Case 5. In this case papillœdema and headache disappeared, only to reappear five weeks later coincidently with the onset of a fresh nasopharyngeal infection. In this case careful inquiry failed to establish any obvious cause for the initial condition, but in view of the occurrence of a "cold" preceding the relapse, it seems reasonable to assume a similar sequence of events on the first occasion, a "cold," or a slight attack of tonsillitis, having possibly occurred at an earlier date. In Case 3 there was clinical evidence of nasal sinus infection during the acute phase, and when the child was admitted to hospital there were signs of subsiding infection of the antrum. Nine months later this patient developed a left otitis media without any return of hydrocephalic symptoms. In the remaining four cases there was no evidence of infection of the sinuses. Radiological examination at a later date in Cases 1 and 3 showed no abnormality. In Cases 2 and 5 there was "slight thickening of the lining membrane of both antra" (Dr. H. Graham Hodgson). A puncture of the right antrum in Case 5 was, however, negative.

With the exception of Case 1 the remainder had never undergone tonsillectomy, and of these four showed evidence of well-marked tonsillar infection.

In three cases in which there was a definite history of a "cold" or "sore-throat" there was an interval of one day to two weeks before the symptoms of hydrocephalus showed themselves. It is probable that although in this series of cases the latent interval appears to have been short, in some cases a longer period may elapse. A possible explanation of this might be that an attack of tonsillitis or nasal catarrh caused the patient to become hypersensitive, and that at a later date a minor recurrence was sufficient to produce a condition of allergy with its main effect on the choroid plexus.

These facts suggest that nasopharyngeal catarrh and tonsillitis have a causal relationship to certain cases of toxic hydrocephalus.

Symptomatology.—The picture of raised intracranial pressure develops quickly in the course of a few days, and reaches its maximum after a period varying from one to two weeks. There is then a tendency to improvement with the exception of ocular symptoms, the patients often feeling and appearing in their usual health. This period of what may be called compensation, may be prolonged for some weeks or months. If untreated the papillœdema may persist, or may slowly subside leaving behind varying degrees of optic atrophy with consequent impairment of vision and even blindness. In other cases relapses may occur, usually associated with a fresh infection.

The symptomatology will now be considered in more detail.

Headache is a constant feature, and is the earliest sign of hydrocephalus. In three of the cases the headache was frontal, and in Case 5 it was more severe on the left side. In Case 1 pain at the back of the neck preceded generalized headache, and the head was drawn over to the right. This was the only case in which a history of an abnormal posture of the head was obtained. Case 2 suffered from pain referred to both the frontal and occipital regions. The headache in every case was severe at the onset, and had the usual characteristics of headache associated with increased intracranial pressure. In Cases 3 and 5, the headache disappeared in three and five weeks respectively, and was still absent when they first came under observation. In the remaining three cases the headache decreased in intensity after the first week or two, but reappeared in Cases 1 and 5 with the occurrence of a relapse.

Vomiting.—This occurred only in the three youngest patients. It was a marked feature in Cases 4 and 5, and in the latter case was typically projectile in character. In no case did the vomiting precede the headache. Drowsiness was present in one case only.

Constitutional symptoms.—The three eldest patients, aged 14, 16 and 18 respectively, suffered little or no constitutional disturbance, but were inconvenienced by the headache. In the two younger cases vomiting was found distressing, and both these patients, as a consequence, felt ill. No records of temperature during the first few days were obtainable. Only one patient had a raised temperature for the first twenty-four hours under observation. An important feature of all the cases when first seen was their appearance of well-being.

Ocular symptoms—Papillœdema was present in each case. The swelling varied from 2 to 6 diopters. Case 1 showed the greatest degree; this case was seen for the first time five months after the onset. Impairment of vision was noticed by two of the patients, Cases 1 and 5, in the former approximately six weeks, and in the latter case three weeks, after the appearance of headache. Vision was found to be impaired in four out of the five cases when they first came under observation. As one would expect, the reduction was roughly proportionate to the duration of the symptoms. Case 1 illustrates this point. The right vision was $\frac{6}{24}$ and left $\frac{6}{36}$, when she was first seen five months from the onset. The earliest occurrence of failure of vision was three weeks from the onset, in Case 3, vision being right $\frac{6}{18}$, left $\frac{6}{12}$. The impression was gained that in toxic hydrocephalus, owing to the rapidity with which increased intracranial pressure develops, vision is affected earlier and to a greater degree than is usual in papillœdema due to cerebral tumours. The improvement of vision that occurs with subsidence of the papillœdema may be quite rapid.

The *visual fields* showed no distinctive alteration beyond a tendency to generalized constriction. In Case 1 the fields were variable. Initially an atypical right homonymous hemianopic defect was found, but one week later there was a flattening of both fields from above and below. In Case 2, in which vision remained unimpaired throughout, the fields were normal. *Double vision* was complained of by four out of the five patients, and in each case it was due to a paresis of an external rectus muscle; it quickly disappeared after the first few lumbar punctures. *Nystagmus* was present in two cases; in one it was rapid and fine, in the other slow to one side. In two other cases nystagmoid movements were observed.

Remaining cranial nerves.—The 5th cranial nerve was intact. No facial weakness or deafness was observed in any case. The other cranial nerves were normal.

Posture of head.—No abnormality in the position of the head was noticed in any case that could not be accounted for by the diplopia. In Case 1 there was a history of the head being turned to the right soon after the onset. In no case was there any rigidity of the neck or impairment of movement of the head. Suboccipital tenderness was looked for carefully, but could not be elicited in a single case.

Limbs.—In the three youngest patients tone was slightly diminished in the upper limbs, but this was no greater than is usually found in children. No impairment of power in the limbs was found. Each case was carefully scrutinized for evidence for a cerebellar defect, and the usual tests were applied with completely negative results in every case. The gait in two of the patients was hesitant, and this was attributed to the double vision. With regard to the reflexes, a characteristic finding, which was present in four out of the cases, was depression of the upper limb reflexes, whilst those of the lower limbs were normally active. This is a common finding in tumours of the posterior fossa, and usually is attributed to the effects of increased intracranial pressure on the lower cervical roots. In no case was there any change in the reflexes suggesting involvement of the pyramidal tract.

Cerebrospinal fluid.—Symonds has emphasized the characteristic features of the fluid, namely an increased pressure and normal cell and protein constituents. These features were found in each of the cases in the present series. In four of the five cases the pressure exceeded 300 c.c. of water as measured with Greenfield's manometer. In Case 4 the maximum pressure recorded was 280 mm. of water. In Case 3 one specimen of the cerebrospinal fluid contained 13 lymphocytes and 105 red cells. In the remaining cases there was no increase in the number of cells, or in the percentage of protein. In every case the Wassermann reaction was negative. The number of lumbar punctures necessary in each case varied from three in Case 3, to ten in Case 5, but in this last case, as well as in Case 2, in which six were carried out, there was a relapse. The greatest amount of cerebrospinal fluid drawn off at one time was 37 c.c. The effect of the first lumbar puncture was always to relieve headache if this was present. As a rule the cerebrospinal fluid pressure subsided *pari passu* with the lessening of the papillœdema. As judged by the cerebrospinal fluid pressure, the hydrocephalus may subside rapidly. In Case 3, for example, the first puncture showed a pressure of over 300 mm., but two days later the pressure was 120 mm. and a further puncture eight days later showed the pressure to be still normal. The papillœdema in this case rapidly subsided. In Case 2 the papillœdema had not quite subsided on the patient's discharge from hospital, although the cerebrospinal fluid pressure was normal, and was still present four months after the onset. The patient then suffered a relapse following a " cold " and on readmission a pressure of 240 was recorded on two separate occasions. The papillœdema, however, had not increased.

In the remaining cases the cerebrospinal fluid pressure was normal when they left hospital. In Case 5 the papillœdema had subsided and the cerebrospinal fluid pressure was normal before discharge. Five weeks later, following a " cold," cerebrospinal fluid pressure was once more raised to over 300 mm. with an increase in papillœdema. This case illustrates well the rapidity with which the hydrocephalus may develop; namely, in the course of a few days.

The flow of fluid was always free, and this is an important point in the distinction between this group of cases and those with an arachnoiditis of the posterior fossa.

Treatment.—Lumbar puncture, as originally advised by Quincke in the treatment of serous meningitis, is the method of choice. In the first three cases this procedure and the use of hypertonic saline were the sole methods of treatment. On theoretical grounds, lumbar puncture would appear to be dangerous in the presence of a high-grade papillœdema, but in these cases, provided care is exercised, no ill-effect has been observed. In Case 4, in which the diagnosis was obscured by a head injury, a ventriculogram was carried out. This was followed by lumbar punctures. In Case 5 the diagnosis was also in doubt, and the same procedure was followed. In these doubtful cases, once the diagnosis of an external hydrocephalus has been established, lumbar puncture can be carried out with impunity. Certain precautions should be observed during drainage by the lumbar sac. Measurement of the pressure is essential on each occasion. If, as is usually the case at the onset, the pressure exceeds 300 mm. of water, then enough fluid should be withdrawn to lower it to approximately half of the initial figure, e.g. 150 mm. of water. The time occupied by the drainage should be at least half an hour. The rate of flow can easily be controlled by half turning the cock on the shaft of the needle. Headache appearing during the drainage should be a signal that the fluid is being withdrawn too quickly, and the flow should be discontinued for a quarter of an hour and resumed more slowly. With regard to the frequency of lumbar punctures, this varies from case to case. When the cerebrospinal fluid pressure remains high, the procedure must be repeated at least every third day until the pressure begins to fall; the interval between the punctures may then be lengthened. It is desirable to obtain a normal reading before discontinuing the treatment, but this may not always be possible. The vision should be recorded at least twice a week, so as to observe the effect of treatment. If the cerebrospinal fluid pressure continues to remain high and papillœdema persists, despite treatment of the "focus" and adequate lumbar drainage, then ventricular tapping should be resorted to to make certain that an internal hydrocephalus is not developing. If this be absent, a further two or three lumbar punctures should be carried out. As long as the papillœdema remains low-grade and vision is not impaired, a waiting policy may be adopted for some months. During this time the patient must be seen every two weeks, the fundi examined and the vision recorded. If at the end of this period the cerebrospinal fluid pressure still remains much raised and vision is failing, then a subtemporal decompression should be resorted to, or if there is any evidence of a developing obstruction, a cerebellar decompression, in the hope of removing any adhesions that may be present in the region of the roof of the fourth ventricle.

Treatment of the infective focus.—It is important that any focus of infection should be treated promptly. If there be an aural discharge, then mastoidectomy should be carried out without delay. Nasal sinus infection should be dealt with, either conservatively, or by puncture, according to the type of case. In the group of cases described in this paper, in four of them it is probable that tonsillar infection played an important part. I believe that in such cases enlarged and unhealthy tonsils should be removed as soon as the more urgent symptoms have subsided.

Results of treatment.—In the series of fifteen cases of serous meningitis reported by Davidoff and Dyke [3], thirteen were treated by subtemporal decompression, and one case had a suboccipital decompression. The symptoms cleared up and there was improvement or arrest of the failing vision. After leaving hospital they were followed for periods varying from a few months to several years. Dehydration methods were continued at home. Final disappearance of the papillœdema required from six months to several years. There was occasional return of headaches. The results in my small series of five cases treated by spinal drainage are as follows: Each of them have definitely recovered from the hydrocephalus, headache and papillœdema being no longer present. The vision is full in three cases. In Case 1, which did not come under observation until five months after the onset, there is a mild degree of post-neuritic atrophy, and vision two and a half years later is now, right $\frac{6}{12}$, left $\frac{6}{9}$, with an associated moderate degree of post-neuritic atrophy. Two years have passed since Case 2 was first seen and the vision remains full. In Cases 3 and 4, twelve months and six months respectively have elapsed. Since their discharge from hospital Case 3 subsequently developed signs of Hodgkin's disease and more recently a streptococcal otitis media which cleared up without any return of hydrocephalic symptoms, vision remains normal; Case 4 is well and at work, vision being $\frac{6}{6}$ both eyes; in Case 5, the papillœdema disappeared rapidly, only to reappear again one month later. It has subsided much more slowly but is now no longer measurable three months after the relapse. Vision up to the present remains normal.

In these last three cases final pronouncement on the diagnosis and results of treatment must wait another year or two. However, the results up to the present have been favourable, not only from the point of view of the relief of the hydrocephalus, but also of the preservation of vision. They would suggest that if the diagnosis of a toxic hydrocephalus can be established, then lumbar puncture is a safe and efficient method of treatment. In those cases where there is a doubt as to the diagnosis, then ventricular estimation should be carried out, and if this confirms the absence of an internal hydrocephalus, then no further operative interference should be necessary.

Finally, it must be emphasized that careful watch should be kept on these cases for some months after their discharge from hospital.

Only in this way will it be possible to detect relapses and ensure the correctness of the original diagnosis.

DIFFERENTIAL DIAGNOSIS.

The rapid development of a hydrocephalus in a young person may lead to considerable diagnostic difficulties. There are three conditions with which toxic hydrocephalus may be confused: (1) An abscess; (2) a tumour of the posterior fossa; (3) an arachnoiditis of the posterior fossa. With regard to an abscess, this is likely to prove a matter of difficulty only when an otitis media is present. Symonds has dealt fully with this aspect of the subject in his paper on "Otitic Hydrocephalus." Arachnoiditis of the posterior fossa, although a less common condition than a tumour, will be considered first. Howell [4] emphasizes that the clinical picture will depend on three factors: (*a*) The area involved; (*b*) whether or not an encysted collection of fluid has formed; (*c*) whether hydrocephalic dilatation of the ventricles has resulted from blocking of channels through which the cerebrospinal fluid circulates. In France Claude [2] and others have studied the various clinical problems arising from these three different factors. Claude stresses the importance of the following signs due to a localized collection of fluid in the posterior fossa: (1) Occipital headache aggravated by movement, effort or vomiting; (2) stiffness of the neck; (3) giddiness and unsteadiness in walking; (4) papillœdema which, however, is not constant; (5) preservation of hearing until a late stage. It would appear that stiffness of the neck, on which Claude lays stress, should be the most helpful sign in differentiating this condition from toxic hydrocephalus. In Case 1 it was probably present in the initial stage, as there was occipital pain and the head was turned to one side. This sign was, however, absent in the remaining cases when they came under observation, and there was no history suggesting that it had ever been present.

When there is a generalized arachnoiditis of the posterior fossa, the signs are more diffuse. According to Barré [1], multiple cranial nerve involvement, usually bilateral, is characteristic; there may be an irritative phase at first, followed by paresis. Cerebellar and pyramidal signs are slight, or may be absent. To this local picture are added signs of an internal hydrocephalus.

When symptoms of focal disturbance in the posterior fossa arise with or without signs of a hydrocephalus, the condition is more likely to be confused with a tumour than with a toxic hydrocephalus. There is, however, one type of arachnoiditis of the posterior fossa which may be impossible to distinguish from an external hydrocephalus without the aid of ventriculography, namely, that form in which adhesions affect chiefly the region of the roof of the fourth ventricle, causing an obstructive hydrocephalus. The following is an example of this condition :—

Case 6.—*Female, aged* 9. *December*, 1936, *headache, vomiting, double vision and impaired eyesight. One month later, no headache, high-grade papillœdema, reduced vision, external rectus palsy, no localizing signs. Ventriculograms revealed bilateral internal hydrocephalus. Suboccipital exploration. Arachnoiditis. Secondary infection. Death.*

B. L., Reg. No. A.3398. Referred to the writer by Dr. Alan Moncrieff on January 28, 1937. Admitted Neurological Ward, Middlesex Hospital, on the same day.

History.—According to her mother this child was in good health until December 22, 1936, when she complained of headache over the left eye. The headache was intermittently present until December 27. On that day she vomited and appeared tired and drowsy. On the following few days the headache and vomiting continued and the child did not seem so well. She was seen by a doctor on December 31. He ordered her to bed where she remained until January 3, 1937. By this date the vomiting had stopped and the headache was less severe, but she complained of pains at the back of the neck and across the shoulders. On getting out of bed she appeared unsteady, and on the following day she complained of some failure of vision of the left eye, and also saw double. On January 6 she received some medicine which caused the headache to disappear, and it only recurred once or twice prior to her admission to hospital on January 28. She had not been subject to "colds" until 1936, when one occurred in the spring and the other at the beginning of October. There was no history of discharge from the ears. Early in December, 1936, she fell and hurt her head, but this did not seem to affect her.

Past history.—She had whooping-cough at the age of 2½ years. She had never undergone tonsillectomy.

Examination.—On admission on January 28, 1937, temperature 98·2° F., pulse 96, respirations 24. She did not complain of headache. She was a bright, intelligent child, and she did not seem at all ill. There was approximately 5 diopters of papillœdema in either eye, with a few small recent hæmorrhages around the right disc. The visual fields were generally constricted. Vision in the right eye was $\frac{6}{18}$ partial, and in the left eye $\frac{6}{36}$. The pupils were dilated and both reacted sluggishly to light. Fine lateral nystagmus was present to either side. Intermittent paresis of the left external rectus was noted. Hearing was slightly diminished in the left ear, but wax was present; no discharge from the ear was seen. The remaining cranial nerves were normal. The posture of the head was normal, and there was no suboccipital tenderness. Tone was slightly diminished in both upper limbs. Power was good on both sides. Co-ordination was normal, and she showed no tremor or ataxia. The reflexes in the arms were markedly depressed. There was no sensory loss. Abdominal reflexes were brisk and equal on the two sides. In the lower limbs power was good, the deep reflexes were active, the right knee-jerk more so than the left, and the plantar responses were flexor. She walked with undue care, but there was no swaying, and she was able to stand on either leg unsupported. There was no nasal discharge; the tonsils were enlarged and appeared unhealthy. Other systems appeared normal.

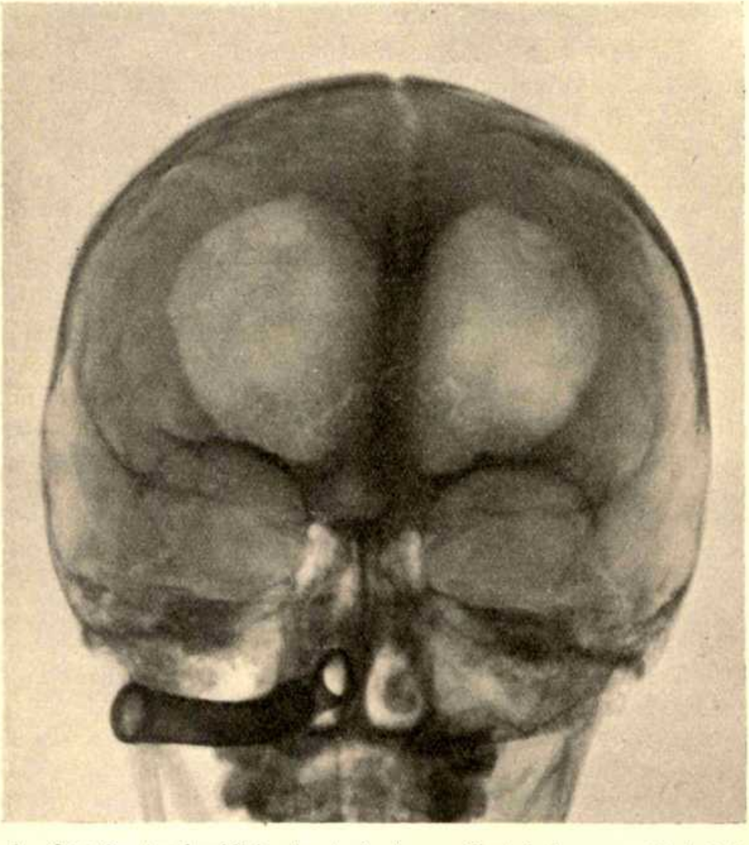


FIG. 2.—*Case* 6. Arachnoiditis of posterior fossa. Ventriculogram. Marked degree of internal hydrocephalus.

The absence of headache and the well-being of the child suggested a toxic hydrocephalus, rather than a tumour of the posterior fossa, although there was no recent history of nasal catarrh or a tonsillitis. In view of the high-grade papillœdema it was decided to perform a bilateral ventricular tap with ventricular estimation, and if there was evidence of dilatation of the lateral ventricles then air should be injected. This procedure was carried out by

Mr. P. B. Ascroft on February 1, 1937. The pressure in the ventricles was found to be very high, e.g. 490 mm. of water. Approximately 90 c.c. of fluid were removed, and air was injected. The X-ray picture showed a well-marked bilateral internal hydrocephalus (fig. 2). The 3rd ventricle did not show up well and the 4th ventricle not at all. Air was released from the ventricles two hours later.

It was now clear that we were not dealing with an ordinary case of toxic hydrocephalus, but presumably with an obstructive lesion of the iter, or of the 4th ventricle, due either to arachnoiditis of the posterior fossa, or to a mid-line tumour. The abrupt onset of symptoms of increased intracranial pressure, followed by subsidence, and the absence of any focal signs, made the diagnosis of a tumour less likely than that of an arachnoiditis. On February 2, 1937, Mr. Ascroft performed a cerebellar decompression. Repeated ventricular tapping was necessary during the first part of the operation, owing to the high pressure. The dilated 4th ventricle was opened, resulting in a great gush of cerebrospinal fluid. Adhesions were found and divided. From their position in relation to the foramina, it was certain that they were blocking the roof of the 4th ventricle. Unfortunately, the child persisted in scratching the region of the burr holes, a streptococcal infection developed which spread to the ventricles, and despite the use of Prontosil, death from meningitis resulted eight days after the operation. A post-mortem was refused.

If the history of this case and that of Case 5 be compared, the striking similarity between them is apparent.

Theoretically, at least, lumbar puncture and the application of Queckenstedt's test, with information gained as to the rate of flow and the amount of cerebrospinal fluid obtained, should enable a diagnosis to be made between an obstructive and an external hydrocephalus. Such a step, however, may be dangerous should the hydrocephalus be of the non-communicating type, and therefore it is much safer to carry out bilateral ventricular tap with estimation of the pressure and amount of fluid in the lateral ventricle, followed, if necessary, by ventriculography. The injection of a colouring matter into the ventricle, followed later by lumbar puncture, can be done if there is doubt about the size of the ventricles, or if ventriculography is, for any reason, impracticable.

Tumours of the posterior fossa.—The differentiation of a toxic hydrocephalus, in the absence of an obvious focus of infection, from a tumour of the posterior fossa, more especially of the cerebellum or 4th ventricle, may be impossible on purely clinical grounds. However, careful attention to certain details in the history may be helpful in those cases where physical signs are scarce. As a rule, the clinical picture of a tumour in this situation is characterized by slow progression. Headache, for example, due to a cerebellar tumour may at first be intermittent, increasing in severity as the weeks pass, contrasting with the initial severe headache of a toxic hydrocephalus, which diminishes or even disappears after the first two to three weeks. Again, double vision, when it occurs in a toxic hydrocephalus, does so within the first three weeks as a rule, whereas its appearance in a cerebellar tumour is usually later. In the case of a cerebellar tumour, repeated examination will usually reveal some evidence of inco-ordination in the limbs or in walking, which is lacking in a toxic hydrocephalus.

More rarely tumours of the 4th ventricle, or of the vermis, may have an onset which is quite abrupt. Occipital pain radiating down the neck and sometimes into the shoulders, with exacerbations, is characteristic. The neck is usually held stiffly, and the head may be turned to one side or bent slightly forward. Suboccipital tenderness is almost constant. Sudden movements of the head may precipitate bulbar symptoms such as giddiness, vomiting, disturbances of respiration and of pulse, and even syncope. Cerebellar signs are usually found, but are often discrete. They consist of nystagmus, hypotonia and lack of co-ordination, particularly in walking. With the exception of occipital headache and fine nystagmus, none of the above signs are met with in toxic hydrocephalus. However, it may be impossible to distinguish between the two conditions without the aid of ventriculography.

DISCUSSION.

Toxic hydrocephalus is a condition that occurs chiefly in childhood and early adult life. Although its association with otitis media is best known, it is probable that other sources of sepsis, such as sinusitis and tonsillitis, are equally important. More rarely, it may follow one of the infectious fevers. The cases reported in this paper illustrate the part played by nasopharyngeal infection in its causation; the rapid return of symptoms of hydrocephalus that followed a fresh "cold" was a striking feature in more than one case. Unfortunately, no systematized bacteriological investigation of these cases was undertaken. Sheldon [7] has reported a case in which there can be little doubt that a hypersensitivity to a streptococcus was the cause of the hydrocephalus. A woman, aged 23, had an attack of tonsillitis from which she had often previously suffered. Eight days later a scarlatiniform rash appeared, followed by a painful effusion into the joints, and a serous meningitis with four diopters of papillœdema. Both these conditions subsided as a peritoneal abscess due to a hæmolytic streptococcus developed, its drainage being followed by complete recovery. Sheldon comments on the rarity of the association of effusion into the joints and a serous meningitis. He refers to a number of cases dealing with the association of serous meningitis and serum sickness. He considered that in his own case a streptococcal toxin acted directly on the synovial membranes and choroid plexuses, and he draws an analogy between a serous hydrocephalus resulting from an allergic state such as serum sickness, and a similar allergic condition in his own case. His conclusions are of interest in considering the group of cases described in the present paper. Case 1 showed the association of a scarlatiniform rash and a hydrocephalus. Three of the remaining cases indicated clearly the close relationship that exists between nasopharyngeal infection and the onset of the symptoms of increased intracranial pressure. It is of interest to note that Case 4 suffered a year previously from acute nephritis, possibly secondary to a chronic tonsillar infection; Case 3 developed an otitis media nine months after the subsidence of the hydrocephalus, unassociated with a return of symptoms; a pure culture of a hæmolytic streptococci was obtained from the aural discharge. This aspect of the problem requires further study in order to determine whether the same organism, for example a streptococcus, is pathogenic in all these cases, including the group of otitis media.

We know little or nothing of the pathological changes in the brain in this condition. The fact that complete recovery from the hydrocephalus usually takes place leads to the presumption that no permanent changes in the pia-arachnoid occur. However, it seems probable that the clinical distinction between toxic hydrocephalus and arachnoiditis is greater than the pathological one. Infection of the ear, nose and throat plays an equal part in the causation of both these conditions. In arachnoiditis adhesions occur, sometimes associated with an underlying encephalitis or ependymitis, according to certain writers. In toxic hydrocephalus, on the other hand, we suppose that the condition is merely due to a functional disturbance of the choroid plexus. It seems plausible to assume that there are cases which bridge the gap between these two conditions. For example, in the subacute type of toxic hydrocephalus, in which, despite adequate drainage, the papillœdema subsides very slowly and relapses are common, a mild degree of arachnoiditis may develop.

With regard to the type of hydrocephalus, Passot came to the conclusion that it was purely external (hydropisie meningée), firstly from the fact that on lumbar puncture there was an abundant flow of cerebrospinal fluid which relieved the pressure, and secondly because in one case that was operated on, there was a free flow of cerebrospinal fluid when the dura was incised. Confirmation of this view was obtained in two of my cases in which ventricular tapping was carried out. In Case 4 the ventriculogram was normal. In Case 5 the ventricular pressure was only slightly raised; difficulty was experienced in putting air into the ventricles, and the subsequent ventriculograms were failures. These findings definitely excluded an internal hydrocephalus, and along with a negative Queckenstedt's test and free flow of fluid, pointed to an accumulation of cerebrospinal fluid outside the ventricular system. Davidoff and Dyke, in twelve out of their fifteen cases of serous meningitis, performed pneumo-encephalography. In every case the ventricular system was normal in size, shape and position. The authors comment on the high proportion of their cases in which ventriculography failed to show satisfactory filling, which they attribute to the small size of the ventricle and the high intracranial pressure. They believe that these two factors caused the expulsion of air along the needle-track. These findings are important and support Passot's original contention that the condition is one of external hydrocephalus. They enable a clear distinction to be made between toxic hydrocephalus and the type of arachnoiditis of the posterior fossa which causes an obstruction.

The actual cause of the hydrocephalus may be due to over-production of cerebrospinal fluid, or to some difficulty in absorption of the fluid, or possibly to a combination of these causes. It seems clear that the comparatively rapid disappearance of the papillœdema and raised intracranial pressure that may occur as a result of lumbar puncture, precludes the possibility of an actual pathological obstruction to the absorption of the cerebrospinal fluid. On the other hand, the rapid onset of the condition suggests an over-production of cerebrospinal fluid, and as the choroid plexus may be regarded as the source of the fluid, it may be assumed that some alteration in its function takes place, presumably due to the effects of toxins circulating in the blood-stream.

SUMMARY.

The adjective "toxic," is suggested to describe the hydrocephalus that may follow otitis media, nasopharyngeal, and other sources of infection in young persons.

Five cases are described in which a nasopharyngeal infection seemed to be the causal factor.

The results of treatment by spinal drainage are given.

The differential diagnosis from arachnoiditis and tumours of the posterior fossa is discussed.

Evidence is brought forward in support of the view that the hydrocephalus is of the external type, and that it is caused by an overproduction of cerebrospinal fluid.

REFERENCES.

[1] Barré, J. *Rev. Neurol.*, 1933, **1**, 879.
[2] Claude, H. *Ibid.*, 1933, **1**, 824.
[3] Davidoff, L. M., and Dyke, C. G. *Journ. Ment. and Nerv. Dis.*, 1936, **83**, 700.
[4] Howell, C. M. *Proc. Roy. Soc. Med.*, 1936, **30**, 33.
[5] Passot, R. *Thèse de Paris*, 1912-13. Paris: S. Steinheil.
[6] Quincke, H. *Deut. Zeit. f. Nervenheilk.*, 1897, **9**, 149.
[7] Sheldon, J. H. *Lancet*, 1933, **1**, 798.
[8] Symonds, C. P. *Brain*, 1931, **54**, 55.
[9] Warrington, W. B. *Quart. Journ. Med.*, 1914, **7**, 93.

THE AXIS-CYLINDER AS A PATHWAY FOR DYES AND SALTS IN SOLUTION, WITH OBSERVATIONS ON THE NODE OF RANVIER IN THE RABBIT.

BY J. R. PERDRAU.

(From the National Institute for Medical Research.)

THE path followed by certain neurotropic viruses in reaching the central nervous system from the periphery or in infecting a part of that system distant from the portal of entry of the virus (e.g. poliomyelitis) is generally considered to be the axis-cylinder. At any rate such is the obvious interpretation of certain observations in experimental infections (Fairbrother and Hurst, 1930). But no proof has yet been forthcoming that the axis-cylinder and not some other constituent of the nerve fibre is the actual pathway followed by even such a small virus as that of poliomyelitis (size about 10 mμ.).

The following experiments were therefore undertaken in order to determine whether substances easily recognized by their colour can travel along the axis-cylinder in the living animal. In addition, similar experiments were made with pieces of nerves and spinal cord obtained from animals immediately after death.

METHODS.

The sciatic nerve of the rabbit was used for the majority of the experiments, but a few isolated observations were also made on the nerves of frogs, guinea-pigs, &c. The sciatic nerve of a rabbit under deep dial anæsthesia was cut, preferably with a very sharp knife in order to avoid crushing the nerve, and one end of the cut nerve, usually the proximal, for a distance of 5 mm. rested in a solution of the the dye in Ringer's fluid. A piece of glass tubing 10 cm. long, bent to a right angle at a point 2 cm. from one end contained the dye. The short limb was closed by a thin piece of rubber sheeting tied over it and perforated by a short piece of capillary tubing through which the nerve was threaded. It is best to close the free end of the tube to avoid siphoning. The wound can be closed over such an apparatus. Kinking of the nerve or pressure of any kind must be avoided. The dyes used

PLATE VII.

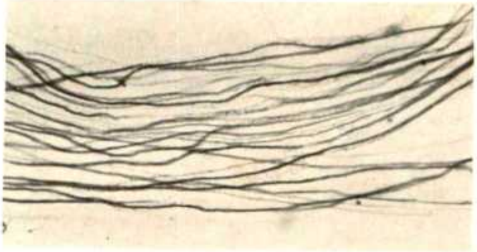


FIG. 1.

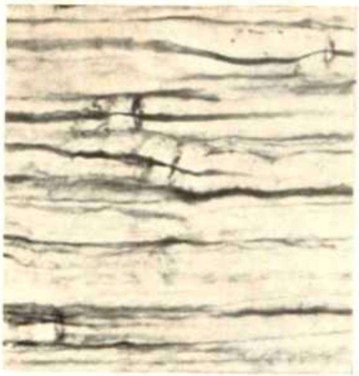


FIG. 2.

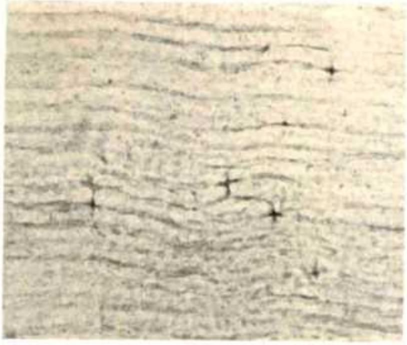


FIG. 3.

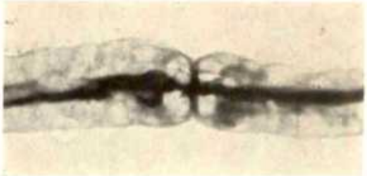


FIG. 4.

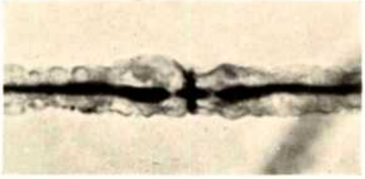


FIG. 5.

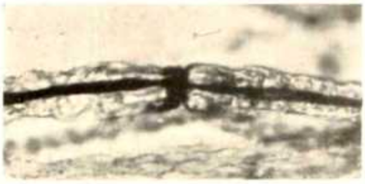


FIG. 6.

FIG. 1.—Rabbit sciatic, excised and impregnated through one end only with methylene blue. The nodes are not seen. × 100.

FIG. 2.—Rabbit sciatic, excised and impregnated by cataphoresis with the P.B. mixture (see text). Rings round the myelin sheath at the node. A first stage in the separation of two contiguous segments of myelin. × 450.

FIG. 3.—Rabbit sciatic impregnated in the living animal with the P.B. mixture. Crosses mark the nodes, the internode being only faintly stained. × 220.

FIGS. 4 and 5.—Rabbit sciatic, excised and impregnated by cataphoresis with the P.B. mixture. In fig. 5 the nerve was not fixed with formalin as usual and the myelin is severely damaged. × 450.

FIG. 6.—Same as fig. 5 (not fixed). One segment of the myelin sheath at the node is more heavily impregnated than the other. × 450.

To illustrate paper by J. R. Perdrau.

PLATE VIII.

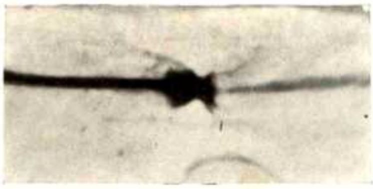


FIG 7.

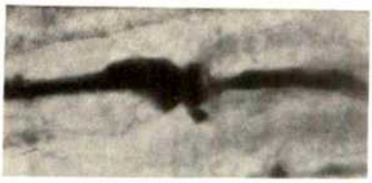


FIG. 8.

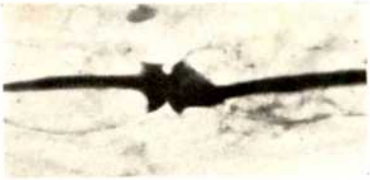


FIG. 9.

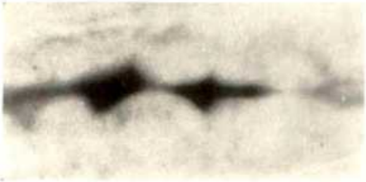


FIG. 10.

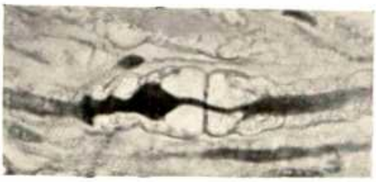


FIG. 11.

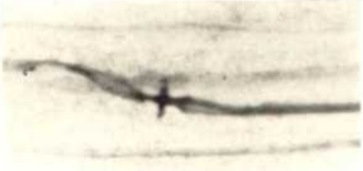


FIG. 12.

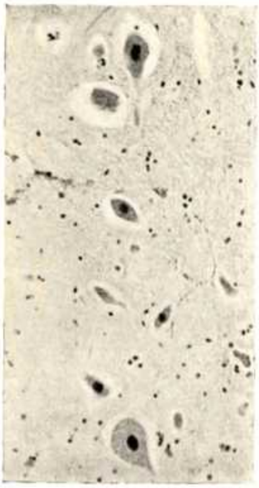


FIG. 13.

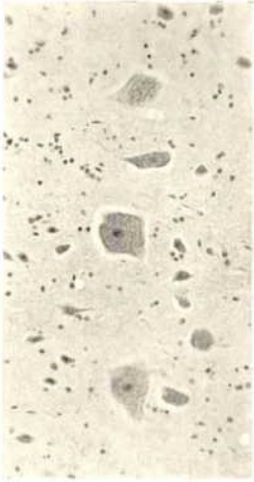


FIG. 14.

FIGS. 7, 8 and 9. Same as figs. 4 to 6, but fixed in formalin. Three nodes at the final stage of separation of two contiguous segments of myelin from each other. × 450.

FIG. 10.—Same as fig. 3. Only half of a "renflement biconique" of Ranvier is seen. × 900.

FIG. 11.—Same as fig. 4. Paraffin section showing thinness of axis-cylinder at the node with a swelling just beyond caused by stretching the nerve. × 450.

FIG. 12.—Same as fig. 3. Swellings on axis-cylinder as the result of stretching a lightly impregnated fibre. × 450.

FIGS. 13 and 14.—Excised piece of spinal cord impregnated by cataphoresis through the sciatic nerve. In fig. 13 the dark nuclei contain Prussian blue, which had not yet reached the cells seen in fig. 14. Counterstained with alum-carmine. × 105.

To illustrate paper by J. R. Perdrau.

have been chiefly methylene blue and acid fuchsin, but it is very difficult to obtain permanent preparations with such easily soluble dyes. The nerves were teased immediately after removal and mounted in melted gelatine with or without a piece of cellophane acting as a coverslip. The gelatine is allowed to dry quickly, at 37° C. for preference.

The Prussian-blue method is far preferable and allows of fixation for any length of time, and sections (frozen, paraffin, &c.) as well as teased preparations are possible. Frozen sections and teased fibres should be mounted in such a way that the whole preparation is dry within a few hours, otherwise the Prussian blue will begin to "run". Paraffin sections can be mounted in balsam in the ordinary way. A counter-stain such as alum carmine, safranin or eosin is sometimes useful.

For the Prussian-blue method mixtures of equal parts of 10 per cent. potassium ferrocyanide and of 10 per cent. iron ammonium citrate in Ringer's fluid were used. Fixation was carried out in 10 per cent. formalin in saline containing a little hydrochloric acid (not more than 1 per cent.).

This mixture of potassium ferrocyanide and iron ammonium citrate (subsequently referred to as the P.B. mixture) has been called true Prussian blue by some. This is erroneous as the Prussian blue is only formed after acidifying the mixture. The substances which are present in the mixture, and which impregnate the nerve, are in true solution and pass through a gradocol membrane of an average pore diameter of 5 mμ. Colloidal Prussian blue purified by dialysis after acidifying with oxalic acid, cannot be substituted for the mixture.

For resected pieces of nerves, still attached or not to the spinal cord, various methods were used. The nerve can be suspended in a tube containing a little of the dye in solution or of the P.B. mixture, and liquid paraffin is floated on top so that only 2 or 3 mm. of the nerve lie in the solution. The liquid paraffin prevents evaporation, especially when the nerve is wrapped in gauze wetted with Ringer's fluid.

For the cataphoresis experiments non-polarizable electrodes were used with a 12 volt battery ($\frac{1}{2}$ to 1 milliamp). The nerve was again kept moist during the whole of the experiment. As all the substances used in these experiments are negatively charged, they were connected up to the kathode. One feature of great importance in all these experiments is that no pressure of any kind should be applied to the nerve. For instance, the pressure produced by a drop of melted vaseline which is allowed to solidify round the nerve in order to obtain a waterproof joint is enough to frustrate the object of the experiment.

THE AXIS CYLINDER.

Both in the living animal and with isolated pieces of nerve, the dye or the P.B. mixture will permeate the axis-cylinder selectively, with great ease at first but more slowly afterwards, for a distance of 4 to 5 cm. in about four hours (Plate VII, fig. 1). The connective tissue sheaths will also take up the dye, the perineurium heavily, but Henle's sheath only lightly. The axis-cylinders do not all take up the dye equally well. As a rule the largest fibres are the most heavily stained whilst the intensity of the colour diminishes the further the dye travels. Little difficulty was therefore encountered in demonstrating that certain substances in true solution travel easily and apparently selectively along the axis-cylinder. In order to make sure that the dye or the P.B. mixture did not reach the axon by any other way, pieces of nerves were firmly ligated at both ends and allowed to soak in the substances used. If the perineurium is intact the axon remains colourless. In Dogiel's method of demonstrating nerves in thin layers of tissues which are immersed in a solution of methylene blue, it is quite likely that the dye has travelled up the axis-cylinder from its cut end.

On the whole, therefore, the results obtained in the experiments now reported agree with the modern view that the consistency of the axis-cylinder is that of a soft jelly (de Rényi, 1929).

Permeation is considerably increased in intensity and in extent by the use of a weak electric current (cataphoresis). Positive results have only been obtained so far with substances in true solution. With colloidal preparations such as Prussian blue and Victoria blue not a trace of impregnation of the axis-cylinder has ever been obtained. Congo red and carminic acid in cataphoresis experiments have given slight staining of the axis-cylinder for a distance not exceeding ¾ cm., but these experiments have been too few to allow of any deductions being drawn from them. These colloidal dyes precipitate very quickly in Ringer's fluid, and no better results were obtained when a little protein was added to them. Distilled water as the solvent produces undesirable changes in the nerve fibre.

NODES OF RANVIER.

Apart from the fact that substances in true solution are capable of spreading along the axis-cylinder, some other interesting observations on the nodes of Ranvier were also made, particularly with the P.B. mixture. As already stated, this mixture travels not only along the axis-cylinder, but also along the connective tissue sheaths. The perineurium is usually an intense blue and is easily dissected off. Henle's sheath is a pale blue and is in sharp contrast with the deeper colour of the axis-cylinder. In cataphoresis experiments the neurilemma and occasionally the network of neurokeratin in the myelin sheath are also faintly outlined.

At the nodes the P.B. mixture has the property of separating any two contiguous segments of myelin from each other, and various stages of this process can sometimes be seen in a single preparation. With methylene blue, on the other hand, one sees only a continuous axis-cylinder without any cross-pieces of any kind (fig. 1), in fact it is extremely difficult in mounted preparations to recognize the site of the nodes. The external outline of the myelin sheath looks continuous without even a depression at the nodes.

With the P.B. mixture the junction between any two segments of myelin is quickly revealed, because the joint is rapidly permeated both from the side of the axis-cylinder and from Henle's sheath, so that on acidification the site of the node becomes obvious. A depression appears on the surface of the myelin sheath and a blue ring is often seen there (Plate VII, fig. 2). At the same time the mixture extends into the joint from the axis-cylinder and if this has gone far enough the classical appearance obtained with silver nitrate is reproduced (fig. 3). A longitudinal section of the nerve at this stage shows blue crosses at the nodes with an unstained or lightly stained internode. This does not mean that the axis-cylinder at the internode does not contain the P.B. mixture, but rather that the acid has not been able to penetrate so far and precipitate the Prussian blue.

The further stages of what happens at the nodes are best observed in cataphoresis experiments. The cross-pieces thicken and shorten (figs. 4 and 5) as the depression on the surface deepens until ultimately the contiguous surfaces of any two adjoining segments of myelin become separated (Plate VIII, figs. 7 to 9). These surfaces now adopt a rounded appearance and become more intensely impregnated. A careful study of the nodes at this stage gives the impression that the myelin sheath is not so firmly adherent to the axon at the node as it is at the internode and is loosened from its attachment by the P.B. mixture. One gains an impression of two funnels facing each other with the axis-cylinder in the centre. This appearance may be an exaggeration of the "renflements biconiques" of Ranvier, which are frequently seen in these preparations and which may be an earlier stage of one and the same process, that is to say, of the lifting of the myelin sheath from the axis-cylinder at the node. The "renflement biconique" of Ranvier may sometimes consist of a single cone (fig. 10), one segment of myelin having apparently lifted up from the axis-cylinder before its immediate neighbour.

Another point which is well demonstrated in these preparations is the thinness of the axis-cylinder at the node (fig. 11).

The accompanying photographs do not give the gradations in colour which one sees under the microscope since very thin preparations are only possible after embedding in paraffin wax and also because cellophane is quite unsuitable for photomicrography. Fixation in formalin is responsible for the small cross-sectional area of the axis-cylinder as compared with that of the myelin sheath.

Certain artifacts are inevitable, especially owing to the necessity of mounting in gelatine. The outline of the myelin sheath in unfixed preparations (figs. 5 and 6) is often wavy. Swellings on the axis-cylinder (figs. 11 and 12) are common in teased preparations, especially in lightly impregnated fibres. A heavily impregnated fibre such as one obtains in cataphoresis experiments usually retains a uniform outline (figs. 6 to 9) even after teasing. These swellings, which are well known with other methods of demonstrating the axis-cylinder are never seen in the thin nodal portion where the axis-cylinder is denser than elsewhere (de Rényi, 1929) and is therefore more resistant to stretching. The incisures of Schmidt-Lantermann are not revealed in these preparations, but the neurokeratin network, as already stated, is often faintly outlined in heavily impregnated fibres.

On the whole, therefore, by the use of the Prussian-blue method the underlying principle on which the nodes of Ranvier in the rabbit are constructed can be shown to be similar to that which obtains in the frog. In the latter the failure of the segments of myelin to meet at the node as well as the incisures of Lantermann can be easily demonstrated in a teased preparation.

Many of the stages described and figured in this paper are well known. That these stages are a continuous process as the result of certain manipulations adopted for the demonstration of the node it is the object of this paper to show.

EFFECT ON THE NUCLEUS OF THE NERVE CELLS.

If a piece of spinal cord (e.g. lumbar) with one anterior root still in position is impregnated through that root by cataphoresis, the Prussian blue will be found on acidifying to have accumulated almost exclusively in the nuclei of healthy cells of the anterior horn which have not been altered by the conditions of the experiment. The axis-cylinder has been traced almost continuously on rare occasions from the surface of the cord to the cell. The chromatin in these cells is intensely coloured (compare figs. 13 and 14) but the nucleolus and cytoplasm as well as the tigroid substance remain unstained and can be counterstained with alum carmine, pyronin, etc. Cells which are obviously altered as the result of the various manipulations are often stained a uniform blue.

If a piece of cervical cord (e.g. C_8) is used where the anterior and posterior roots unite immediately on emergence from the cord and where the posterior root ganglion is firmly adherent to the cord, the nuclei of the ganglion cells, as a rule, do not take up the P.B. mixture, but the cells of the cord itself do. The explanation for this difference in behaviour may be found in the peculiar mode of entry and of exit of the axis-cylinder from the cells of the ganglion, so that the P.B. mixture rarely reaches the neighbourhood of the nucleus. Whatever the explanation may be for the presence of the Prussian blue in the nucleus, it is not suggested here that the axis-cylinder has any direct connection with the nucleus. It may be mentioned incidentally that the presence of neurofibrils in the axis-cylinder of the rabbit is not revealed by these methods of impregnation.

CONCLUSIONS.

(1) Dyes such as methylene blue and acid fuchsin and also a mixture of potassium ferrocyanide and iron ammonium citrate travel up the axis-cylinder in the living rabbit as well as in resected pieces of nerves. Cataphoresis greatly enhances the process, but the slightest pressure on the nerve or simple kinking stops the impregnation.

(2) Only salts in true solution behave in this way. Colloidal substances tested up to now, such as Prussian blue and Victoria blue, do not.

(3) The mixture of potassium ferrocyanide and iron ammonium citrate, in contradistinction to methylene blue, reveals the nodes of Ranvier, and if its action is sufficiently prolonged it leads to a separation of the myelin sheath into sections which meet at the nodes, where the myelin is less firmly adherent to the axis-cylinder than it is at the internode.

(4) The "renflement biconique" of Ranvier as well as the cross are probably early stages of this process of separation.

(5) The modern conception of the axis-cylinder as a soft jelly, except

at the node where it is denser and thinner, is supported by these observations.

(6) If the nerve cells of the spinal cord are impregnated through their axis-cylinders by the Prussian blue method reinforced by cataphoresis the nuclei only will be coloured blue. In the posterior root ganglia the nucleus like the rest of the cell body is usually colourless. In altered cells the Prussian blue may be found in both the nucleus and the cytoplasm.

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REFERENCES.

de Rényi, G. S. *Journ. Compt. Neur.*, 1929, 47, 405.
Fairbrother, R. W., and Hurst, E. W. *Journ. Path. and Bact.*, 1930, 33, 17.

THE ORIGIN OF THE RAISED PRESSURE OF THE CEREBROSPINAL FLUID WHICH ACCOMPANIES SUBTENTORIAL TUMOURS.

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IT has been known since the classical experiments of Dandy and Blackfan [9] that obstruction of the aqueduct of Sylvius causes an accumulation of cerebrospinal fluid and a dilatation of the chambers and channels anterior to the block. Dandy and Blackfan were also able to produce hydrocephalus by occluding the subarachnoid space of the midbrain at the level of the tentorium cerebelli. The hydrocephalus developed as rapidly as that which followed occlusion of the aqueduct.

Although an intracranial tumour may occasionally invade and directly occlude a main cerebrospinal fluid channel, such an occurrence is generally admitted to be unusual.

Hodgson [14] investigated twenty-four cases of subtentorial tumours by combined ventricular and lumbar puncture. He found that "sixteen, or two thirds, showed block in some degree and one third did not show any block. Of twenty-one supratentorial tumours block, on the contrary, was absent in nineteen, slightly questionable in one, and definitely present in only one of these cases, a pinealoma." The absence, however, of a communication between the ventricular and the lumbar needle does not, as Stopford [20] has pointed out, prove the existence of an obstruction to the aqueduct; the obstruction may be at the foramen magnum. Stopford investigated a series of five subtentorial tumours. In each instance the signs of intracranial pressure had appeared early and were profound. He concluded, as a result of a careful examination of the brains after death, that it was unlikely that there had been any obstruction to the normal circulation of cerebrospinal fluid in at least four of the five cases.

Masserman and Schaller [17] quote a personal communication from F. L. Reichert in which the latter worker states that he had occasion to insert ventricular, cisternal, and lumbar needles preceding a craniotomy on a patient with a tumour of the brain. The site of the tumour and the pressure of the cerebrospinal fluid were not stated. Reichert, however, "noted that the horizontal pressure readings at the three loci remained equal under various manipulations."

Masserman and Schaller studied the mechanical effect of artificial tumours in different parts of the brain on intracranial hydrodynamics. Observations were made on three cadavers. The intracranial pressures were maintained by artificial means. The tumours were produced by injection of 20 to 40 c.c. of melted paraffin wax in various regions inside the skull. The distortion so produced in the frontal or occipital regions had no apparent effect on the fall of ventricular or cisternal pressure when the fluid was removed by lumbar tap. "When 30 c.c. of wax were injected into the left cerebellar lobe, a partial block between the ventricular and lumbar spaces was effected. Subsequent examination showed the paraffin to have forced the left cerebellar lobe down against the bulb, partially obliterating the fourth ventricle and basal cistern." Encephalograms revealed no evidence of elevation of the tentorium.

According to Paton and Holmes [19], the papillœdema associated with cerebral tumours is caused by a compression of the central vein of the retina and the accompanying lymphatics as they pass from the optic nerve across the subarachnoid space of the optic sheath. They believe that the vessels are compressed as a result of the raised pressure of the cerebrospinal fluid in the subarachnoid space of the optic sheath. It would seem highly improbable that a raised cerebrospinal fluid pressure could be maintained in this space unless it were in communication with the ventricular system (Brain and Strauss [8]). It would appear justifiable to conclude, on the basis of this theory, that the subarachnoid space of the optic nerve must have been in communication with the ventricular system during some period in the development of all intracranial tumours which are accompanied by papillœdema.

Baurmann [1] has reported experiments which would seem to support the conclusion of Paton and Holmes that the central vein of the retina is compressed as a result of the raised pressure of the cerebrospinal fluid in the subarachnoid space of the optic sheath. He found a direct relationship between the pressure of the cerebrospinal fluid and the pressure in the veins on the nerve head. He took as his criterion of the venous pressure the intra-ocular pressure at which the veins on the nerve head first began to pulsate. The intra-ocular pressure was raised by pressure on the eyeball with a gauge of the type devised by Magitot.

Duke-Elder [11] has criticised all the methods in which venous pulsations are used as a criterion of venous pressure. He considers that venous pulsations in the eye are a complicated phenomenon not directly related to the pre-existing intra-ocular pressure.

Baurmann's experiments have recently been repeated on animals by Gibbs [13], who employed a slightly different technique. Baurmann's findings were confirmed. Gibbs concluded, however, that "although it is possible that Baurmann did not measure the true venous pressure, it is certain that he measured something that is a direct and simple function of the venous pressure." It is noteworthy that Magitot [15], and Berens, Smith and Cornwall [7], claim to have found a relationship between the diastolic pressure in the central artery of the retina and the pressure of the cerebrospinal fluid.

The experiments which are to be described were undertaken in an attempt to produce artificial intracranial tumours in dogs and to observe their influence on the pressure and the circulation of the cerebrospinal fluid and on the venous pressure in the torcular. These experiments were limited to a study of subtentorial tumours.

EXPERIMENTAL TECHNIQUE.

The dogs employed in these experiments were mongrels about 2 to 3 years old and weighing from 7 to 8 kilogrammes. Considerable difficulty was at first encountered in devising a suitable technique. Finally, however, the following method was evolved and employed throughout the experiments.

The animals were anæsthetized with intratrachial ether. A transverse incision was made through the skin a short distance behind the external occipital protuberance and the posterior aspect of the occipital bone exposed by a vertical incision along the line of the nuchal ligament. The muscles were retracted with the aid of a mastoid retractor. In the dog, the inferior vermis of the cerebellum is a relatively prominent structure which rests in a depression in the occipital bone called the fossa vermiana. The fossa vermiana usually gives rise to a definite protuberance on the external aspect of the occipital bone which is visible at the bottom of the wound when the muscles are separated. An attempt was made in all experiments to produce a mid-line tumour either in the vermis itself or directly behind the inferior vermis.

A small drill hole is made with a dental bur through the lower part of the protuberance which corresponds with the fossa vermiana. In this region the bone is relatively thin. The aperture is enlarged until a little more than $\frac{1}{8}$ in. in diameter. This can usually be accomplished without injury to the dura which readily separates from the bone. It is, of course, necessary to open the dura if a tumour is desired in the substance of the cerebellum. Tumours in the substance of the cerebellum, however, were difficult to produce successfully and in nearly all the experiments the foreign matter was introduced between the dura and the bone. The tumours were, therefore, extradural in situation.

The most suitable foreign matter for the production of the tumours was ordinary surgical cotton wool impregnated with wax. It was prepared and employed in the following manner. A quantity of paraffin wax melting at 49° C. is placed in an evaporating dish in an incubator set at 55° C. Pledgets of cotton wool, together with a few crystals of carbolic acid, are placed in the melted wax. When required for use, a piece of wool is taken from the dish, as much as possible of the wax squeezed out and the mass shaped while hot to the desired size. The mass is prevented from setting by constant kneading with the fingers. Small pieces of convenient size are now torn from it and are passed with fine forceps through the hole in the occipital bone until the whole of the mass has been treated in this way. It is unnecessary to close the hole in the bone, for the tumour displays no tendency to extrude itself. The muscles are now brought together and the wound closed in the usual way.

With regard to the quantity of material introduced into the cranium, a tumour 0·6 to 0·8 c.c. in volume was found to be the optimum for a dog of the size employed in these experiments. It is interesting to note that the average capacity of the infratentorial space in the fresh skull of a dog weighing 8 kg. is approximately 12 c.c., while the total intracranial capacity is about 75 c.c.

Under ordinary circumstances, the animal appears normal after it has recovered from the anæsthetic and remains symptomless until it is killed six days later. If, however, the tumour has been made excessively large or the cerebellum has been injured during its introduction, the animal may present varying degrees of ataxia. The ataxia is generalized and involves all four limbs and the head. In mild cases the animal walks with its feet set widely apart and there are oscillatory movements of the head. In such a case the condition generally clears up completely in twenty-four to forty-eight hours. In a more severe case the animal is completely ataxic and unable to stand or to support itself in any way. All animals which were unable to stand or walk after a recovery period of twenty-four hours were promptly killed, for they were obviously unsuitable for prolonged observation. In two instances sudden death occurred shortly after the tumour had been introduced. It was considered that the excessive bulk of the tumour had probably led to medullary compression. Occasionally the conduct of the animal made it apparent that it was suffering from severe headache. This was usually observed during the period which immediately followed operation. The headache was considered to be caused by local tension in the dura under the tumour, for it bore no relation to the pressure of the cerebrospinal fluid. Vomiting was not observed in a single instance. An ophthalmoscopic examination was made from time to time in an attempt to detect the onset of papillœdema. Papillœdema was never observed, although the pressure of the cerebrospinal fluid was over 400 mm. normal saline in a number of animals.

At post-mortem examination five to six days after operation, the waxed wool is found to have formed a compact almost spherical tumour which shows little tendency to flatten itself against the bone but projects well forward into the cerebellum. The residual wax prevents the tumour from becoming sodden with blood and exudate. The tumour is adherent to the dura. There is rarely any bleeding although a little fibrinous exudate may be present. On removing the tumour, a circular depression about 1 cm. in diameter and ¾ cm. in depth is observed in the region of the inferior vermis and the adjacent lateral lobes of the cerebellum. The dura underlying the tumour is not adherent to the arachnoid. The arachnoid and the cerebellar cortex immediately beneath the tumour generally appeared normal on naked-eye inspection. The subarachnoid space in this region is almost always free from blood although small subpial hæmorrhages may sometimes be visible. Occasionally a small area of hæmorrhagic softening was present in the interior of the cerebellum. This and the subpial hæmorrhages were probably a result of the trauma which accompanied the introduction of the tumour.

The arachnoid, the pia and the brain substance are to a great extent protected from any irritant action by placing the tumour between the dura and the bone. The cerebrospinal fluid from the cisterna magna, when examined four to six days after operation, was normal in its cell content. Occasionally a slight increase in the total protein content was observed. It is interesting to note that Indian ink, introduced into the subarachnoid space through a needle in the cisterna magna at a pressure only slightly above that of the cerebrospinal fluid, usually found its way to the subarachnoid space in the immediate vicinity of the tumour, although it rarely entered the subarachnoid space directly below the tumour. This was regarded as providing evidence that the tumours did not initiate a spreading obliterative process in the post-cerebellar subarachnoid space. A histological examination of the brains failed to detect any evidence of an inflammatory lesion. Occasionally the arachnoid underlying the tumours presented a slight degree of cellular proliferation. The pia was unchanged. Subpial hæmorrhages when present in this region, were observed to be undergoing changes common to hæmorrhages in the brain. There was rarely any evidence of œdema. The brain and its coverings were unchanged in all other regions.

A careful comparison of brains fixed *in situ* with control specimens never showed the tentorium to be more than slightly raised. The tentorium of the dog is partly ossified. It contains a triangular plate of bone. The apex of the triangle is truncated and forms the posterior border of the incisura tentorii. Its base is firmly attached to the occipital bone along the line of lateral sinuses, where it extends almost as far forward as the petrous-temporal bone. Only the antero-lateral portions of the tentorium are membranous. The ossified portion of the tentorium consists of dense non-flexible bone. Its flexibility was tested on fresh unfixed skulls from which the brain had been removed piecemeal. Pressure was exerted from below and also from above. The bone remained perfectly rigid. If a considerable degree of force was applied, the bone was found to snap rather than bend. It is, of course, conceivable that constant pressure applied for several days may cause some displacement of the bone. The tumours were situated below the ossified portion of the tentorium but were separated from actual contact by part of the cerebellum (fig. 1). The falx cerebri of the dog is not ossified.

An upward displaced tentorium would naturally carry with it the straight sinus and the termination of the great vein of Galen. Careful dissections of brains containing subtentorial tumours which had been fixed *in situ* after injection of the venous system with a carmine gelatine mass, failed entirely to provide evidence that the flow of blood through the great vein of Galen had been obstructed at any point on its course. A careful examination was also made of brains containing a subtentorial tumour which had been fixed *in situ*, but in which the venous system had not been injected with a carmine gelatine mass. It was realized that no matter how carefully the injection be made, there is a risk that the pressure which it is necessary to employ may be sufficient to overcome and to obscure a moderate degree of venous obstruction. Here again, however, no evidence of venous obstruction could be detected.

In a number of experiments the introduction of the tumour was followed by clotting in the torcular. The results from all these experiments were discarded, for it is known that an obstruction to the venous blood in the torcular causes changes in the pressure of the cerebrospinal fluid [5, 6]. Some difficulty was experienced at first in discovering an explanation for this venous clotting, which at times was very troublesome. It was found, after a number of fresh dogs' skulls had been examined, that although the anterior, the posterior and the lateral walls of the torcular consist of strong bone, the floor is often formed by an extremely thin semi-transparent shell of bone. A portion of the cerebellum lies directly below the torcular, and the dura of the posterior fossa is therefore in contact with this thin layer of bone which forms

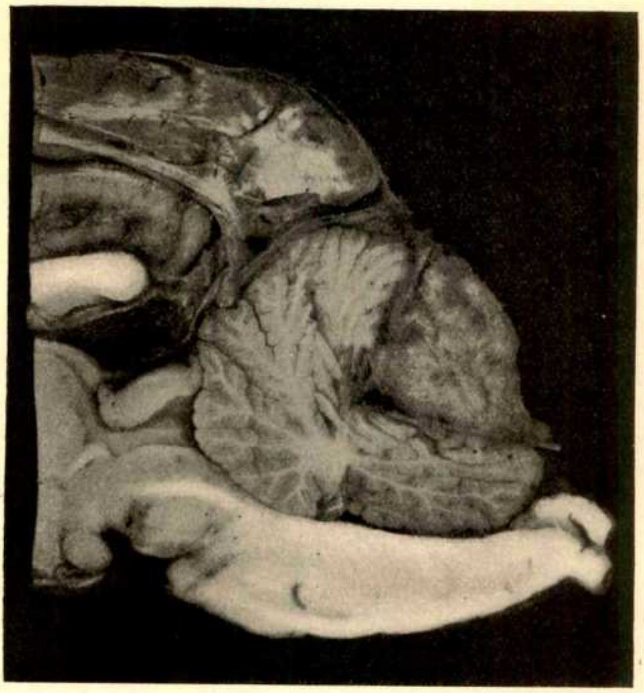

FIG. 1.—A considerably enlarged and untouched photograph of a sagittal section through a brain (Dog No. 20, Table I), containing an artificial subtentorial tumour. The section has passed to the left of the falx cerebri. The brain was fixed in situ and was then removed from the skull. It is improbable, therefore, that the various structures have suffered any displacement. A small quantity of waxed wool has been lost from the posterior aspect of the tumour. The dura underlying the tumour is clearly visible. The dark area below the apex of the tumour is an unusually large subpial hæmorrhage. The great vein of Galen and the straight sinus (the latter has been opened) are clearly visible and it is evident that these structures are in no way compressed. The cerebellum is displaced forward and is indented by the anterior border of the tentorium. A comparison with control specimens reveals no evidence of elevation of the tentorium.

the floor of the torcular. Not infrequently the tumour causes the dura to be stripped from the bone in this region. Under these circumstances, the tumour lies directly below the floor of the torcular and is only separated from the blood in its interior by an extremely thin layer of bone and by the endothelial lining of the sinus. It is not surprising, therefore, that reactive processes are frequently set up in the endothelium which ultimately lead to clotting.

Clotting in the torcular can generally be avoided by taking the precaution to place the tumour so that it does not exert pressure on the bone in this region.

It must be admitted at the outset that tumours produced in this manner cannot be considered identical with neoplastic tumours. They differ mainly in the following ways: (1) While neoplastic tumours may suddenly increase in size as a result of bleeding into their substance or of the onset of acute œdema, their growth for long periods is often gradual and continuous. It is thus possible for them to attain a size which is relatively much greater than that of the maximum quantity of foreign material which can suddenly be introduced into the cranium without serious interference with function; (2) artificial tumours probably produce their maximum effect very shortly after introduction. These effects will become less marked as the brain substance gradually accommodates itself to the mass. This is the reverse of the process which generally obtains with neoplastic tumours. It was the custom, for this reason, to examine the intracranial pressures not later than six days after the introduction of the tumours.

This method of producing intracranial tumours has, therefore, serious limitations. Nevertheless it was hoped to obtain effects which might bear a general resemblance to those produced by neoplastic tumours.

THE EFFECT OF ARTIFICIAL SUBTENTORIAL TUMOURS ON THE INTRACRANIAL PRESSURES.

On the fifth or sixth day after the introduction of the tumours the animals were anæsthetized with ether and a reading taken of: (1) The cerebrospinal fluid pressure in the cisterna magna; (2) the venous pressure in the torcular Herophili; (3) the arterial pressure in the femoral artery. The methods employed to record these pressures have been described in detail in an earlier paper [5]. The results obtained from twenty-one animals are indicated in Table I.

The tumours were extradural in situation and were produced in the manner which has already been described with the exception of Dog

No. 1. In this animal the tumour was intracerebellar and was formed by injecting paraffin wax into the substance of the cerebellum.

(1) *The pressure of the cerebrospinal fluid in the cisterna magna.*—It is difficult to assign an upper limit for a normal cerebrospinal fluid pressure; the pressure varies over a wide range in different animals. The nature of the anæsthetic and the mode of its administration also have a definite influence on the height of the pressure [21, 17]. It would seem that a pressure which exceeds 200 mm. normal saline may generally be regarded as abnormally high. This conclusion has been reached after a study of the cerebrospinal fluid pressure in a large number of normal animals under ether anæsthesia. A standard technique was employed throughout the experiments.

TABLE I.

The intracranial pressures in twenty-one cases of artificial subtentorial tumour. The volume of the tumours was determined after death, and the figures indicate the volume of waxed wool introduced into the cranium. No account, therefore, is taken of exudate or of local œdema of the brain which, when present, will increase the potential volume of the tumour. The pressure of the cerebrospinal fluid and the venous pressure in the torcular are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

Dog No.	Cerebrospinal fluid pressure	Venous pressure in torcular	Systolic pressure in femoral artery	Hydrocephalus	Volume of tumour in c.c.	Post-operative duration of life in days
1	450	85	100	Moderate	1·0	6
2	290	60	110	Moderate	0·8	5
3	300	105	120	Moderate	0·6	5
4	270	90	120	Moderate	0·6	6
5	200	80	140	0	—	6
6	350	105	140	0	0·6	5
7	450	90	130	0	0·7	6
8	280	70	130	0	—	5
9	140	80	130	0	0·4	6
10	120	110	125	0	0·4	8
11	420	120	125	0	0·8	6
12	270	90	110	0	0·7	6
13	270	120	125	0	—	6
14	320	110	130	0	0·7	6
15	350	50	110	0	0·8	6
16	210	120	120	0	0·5	6
17	420	115	120	0	0·7	6
18	330	90	110	0	0·8	6
19	410	80	130	0	0·8	6
20	370	85	120	0	0·6	6
21	280	70	120	0	0·6	6

It will be observed from Table I that the subtentorial tumours have caused in nearly every instance a pronounced increase in the pressure of the cerebrospinal fluid in the cisterna magna. It is noteworthy that it was possible to obtain a reading from the cisterna magna in all experiments. In the later experiments it was the custom to measure also the pressure of the cerebrospinal fluid in the lateral ventricles.

This was easily accomplished by boring a hole through the skull over a lateral ventricle. A gauge 18 needle was then passed down through the dura into the ventricle. The needle was connected with a manometer and the pressure recorded in the ordinary way. The position of the needle and the depth to which it should be introduced were determined from measurements on heads previously fixed in formalin. It was necessary to employ a clamp fixed to the head of the animal in order to maintain the needle steady after its introduction.

The ventricular and the cisternal pressures were always identical. Changes produced in the pressure in the cisterna magna were followed by corresponding changes in the intraventricular pressure, and vice versa.

According to Masserman and Schaller [16], the ventricular-subarachnoid system of the dog differs from that of man in not being able to transmit readily changes in pressure from one portion to another. " Thus if one suddenly raised a dog's ventricular pressure to 75 cm. water, the cisternal and lumbar pressures would climb to the level after a variable interval. Conversely, if a rapid lumbar tap were then done, the curves of intraventricular and intracisternal tension would show a lag of from one to seven seconds before beginning a decline parallel to that of the pressure in the lumbar sac." The lag described by Masserman and Schaller was observed in the animals with subtentorial tumours. It was of varying duration but did not show any marked deviation from that encountered in normal animals. It would appear, therefore, that the tumours had not caused an obstruction of any consequence to the aqueduct of Sylvius.

(2) *Hydrocephalus with artificial subtentorial tumours.*—Hydrocephalus was found in dogs Nos. 1, 2, 3 and 4. It is remarkable that these cases occurred at the beginning of the investigation and succeeded each other. Since then, hydrocephalus has not been encountered in a single experimental animal.

In one instance the tumour was intracerebellar and consisted of wax. In the remaining three cases the tumours were of standard size and were extradural in situation. The technique employed differed in no way from that used in the rest of the experiments. The animals presented no abnormal signs during the post-operative period. It is noteworthy that the pressure of the cerebrospinal fluid in the cisterna magna at the termination of the experiment, was no greater than that in cases uncomplicated by hydrocephalus (Table I). The dilatation of the ventricles was moderate in degree and involved the lateral and the third ventricles. There was, however, slight but definite dilatation of the aqueduct and of the fourth ventricle in all four brains. The cerebrospinal fluid was normal in its cell and protein content, and an histological examination of the brains and of their coverings revealed no evidence of an inflammatory lesion. It is regrettable that the intraventricular pressure was not recorded in any of these animals. It is noteworthy, however, that Indian ink introduced into the cisterna magna in two of these animals spread over the entire cerebral cortex. Indian ink was not introduced in the remaining two cases.

(3) *The venous pressure in the torcular of Herophili.*—The venous pressure in the torcular was always within normal limits. The effect of clotting in the torcular on the pressure in the superior longitudinal sinus will be considered later.

(4) *The systolic blood-pressure in the femoral artery.*—The tumours were without apparent influence on the systolic pressure in the femoral artery.

(5) *The introduction of Indian ink into the cisterna magna.*—A suspension of Indian ink in normal saline solution, about one part of Reeves' Indian ink to four parts of saline solution, was introduced into the cisterna magna before killing the animals. The following procedure was employed when introducing the ink: The suspension, prepared as indicated, was placed in a burette connected with a needle in the cisterna magna. It was the custom to employ for this purpose the needle which had been used to record the pressure of the cerebrospinal fluid. The fluid column in the burette was set either at the exact pressure level of the cerebrospinal level or at a level some 10 to 20 mm. higher. The first method was the method of choice. In this method it was hoped that the minor fluctuations in the pressure of the cerebrospinal fluid which are constantly taking place, would permit some of the suspension to enter the cisterna. It should be borne in mind that if a very small quantity of a relatively strong suspension of Indian ink succeeds in entering the cisterna magna, it will be sufficient to colour, almost immediately, the whole of the cerebrospinal fluid in its interior. The introduction of large quantities of Indian ink is, therefore, unnecessary. The obvious objection to the second method is that a pressure higher than that of the cerebrospinal fluid is employed in order to introduce the ink. In actual practice, however, this method is

probably very similar to the first. The results were identical whichever method was employed.

Replacement methods were also tried, but in view of the observations of Masserman [18] on the effects of drainage of the cerebrospinal fluid on the capacity of the subarachnoid space, they were abandoned as unsatisfactory.

The Indian ink was introduced for periods varying from one to two hours. The volume of fluid introduced varied considerably; good results could be obtained with 1·0 c.c. or even less. As already indicated, it is neither necessary nor desirable to introduce large quantities of the suspension. A careful watch was maintained on the blood-pressure reading in the femoral artery throughout the whole of the experiments. The experiments were discontinued and the readings discarded when the blood-pressure was not maintained.

The animals were killed without disturbing the position of the head by severing the carotid arteries. It was important to remember to cease introducing the Indian ink and to withdraw the needle before killing the animal. The head was removed from the body, the cranium opened and the brain and its coverings fixed *in situ* in isotonic formol saline solution. Occasionally the head was injected with formol saline solution through the carotid arteries. Throughout the whole procedure care was taken to maintain the head with the vertex uppermost. The Indian ink was found to have spread over the cerebral cortex and to have reached the superior longitudinal sinus in every instance when the brains came to be examined. The ink passed freely into the spinal subarachnoid space but only entered the ventricular system in one or two instances.

Similar experiments were conducted on animals without subtentorial tumours. The experiments failed to elicit any difference in the rate of spread of the Indian ink in the normal and in the animals possessing a subtentorial tumour. The following experiment was performed in a number of animals with a subtentorial tumour to exclude the possibility that the spread of Indian ink over the cortex was an agonal or a post-mortem phenomenon.

After the ink had been introduced for an hour, a small trephine hole was made over the convexity of a cerebral hemisphere at a point just external to the superior longitudinal sinus. The ink could generally be seen in the subarachnoid space through the dura. When, however, the dura was opened, the ink was invariably visible in the sulci. These experiments would seem to exclude the possibility that the ink had spread to the subarachnoid space of the convexity of the cerebral hemispheres during the agonal state.

It would seem desirable, at this stage, to consider briefly the possible means by which the Indian ink introduced into the cisterna magna may spread over the cerebral cortex.

(1) The ink will be transported along with the cerebrospinal fluid if this fluid is circulating.

(2) The ink will also spread by simple diffusion. This process, however, will be most evident in the large cisternæ.

(3) The ink may also be dispersed throughout the entire subarachnoid space in the following manner. The volume of the brain at any given moment depends upon a number of factors. For example, a sudden fall in the systemic blood-pressure is followed by a marked shrinking of the brain. Under these circumstances Indian ink will flow from the burette into the subarachnoid space. If, however, the arterial pressure returns to its previous level, most of the ink will be forced out again into the burette. The area coloured by the ink will, nevertheless, have increased considerably. It is obvious that a repetition of this process will gradually cause the whole of the subarachnoid space to be coloured by the ink. It is well known that the volume of the nervous system can be influenced by variations in the intracranial venous pressure or in the osmotic pressure of the blood. Although stringent precautions were taken to maintain conditions as standard as possible throughout the experiments, it is difficult to be absolutely certain that they were entirely successful in any single instance.

It would appear, therefore, that although the introduction of Indian ink into the cisterna magna may be a suitable method for detecting a complete block to the circulation of the cerebrospinal fluid, it is of doubtful value when employed to detect an incomplete or a functional block. An interference with the circulation of the cerebrospinal fluid, brought about by a displacement of the brain, may be regarded as a functional block. It is probable that under these circumstances the obstruction is frequently incomplete or intermittent.

Conclusions based on observations on the circulation of Indian ink may, therefore, be accepted only with the greatest reserve.

(6) *The intracranial pressures associated with subtentorial tumours in which clotting has occurred in the torcular.*—Clotting in the torcular, as already indicated, was a troublesome occurrence. The clot never extended into the superior longitudinal sinus. The straight sinus was always free from clot. Occasionally, however, the whole of the lateral

sinuses were occluded. The venous pressure in the posterior end of the superior longitudinal sinus tended to approximate and sometimes to exceed that of the cerebrospinal fluid. Not infrequently, however, the pressures were identical. The intraventricular pressure was always identical with that in the cisterna magna. The instability of the intracranial pressures was the most characteristic feature of these cases. The cerebrospinal fluid pressure and the pressure in the superior longitudinal sinus showed a marked tendency to fall and to assume a lower level as the anæsthesia was continued. The effect of venous obstruction on the pressure of the cerebrospinal fluid has, however, been described in earlier publications [5, 6] and need not be reconsidered here.

DISCUSSION.

A method has been described by which artificial subtentorial tumours can be successfully produced and their effects studied in dogs. Attention has already been drawn to the limitations of the method and it has been pointed out that the tumours can be expected to have effects which resemble only in a very general way those of neoplastic tumours.

We are now in a position to consider whether these experiments help in any way to explain the origin of the initial rise in the pressure of the cerebrospinal fluid in cases of neoplastic tumours. It is proposed to consider the possible modes by which an experimental tumour may bring about an increase in the pressure of the cerebrospinal fluid.

(1) The tumours may have irritated the coverings of the brain and induced a condition of sterile meningitis. The raised pressure of the cerebrospinal fluid may, therefore, be merely an expression of meningitis and may have no direct connection with the tumours. This possibility merits careful consideration, for the validity of the remarks which are to follow depends upon its elimination.

(2) The actual mass of the tumour may cause a permanent increase in the intracranial pressure by occupying a large proportion of the intracranial cavity.

(3) The tumour may cause an increased production of cerebrospinal fluid either: (*a*) By causing a state of increased venous pressure in the choroid plexuses; or (*b*) in some manner still undetermined. It is obvious that the pressure of the cerebrospinal fluid will not be raised if the absorption mechanism is able to deal with the excess of fluid.

(4) The tumour may interfere with the absorption of the cerebrospinal fluid in the following ways: (*a*) It may cause a main cerebrospinal fluid channel to be obstructed and thus prevent the fluid from reaching

the subarachnoid space of the cerebral hemispheres; (*b*) the tumour may raise the tentorium and cause the cerebral hemispheres to be displaced upwards against the vault of the skull. This may lead to a diminution in the rate of absorption of the cerebrospinal fluid from the whole of the subarachnoid space of the convexity of the cerebral hemispheres; (*c*) it may raise the intracranial venous pressure and thus interfere with the absorption of the fluid into the blood-stream.

It is proposed to discuss each of these possibilities in turn:—

(1) The tumours were foreign bodies and as such were bound to produce some degree of local irritation. In order to reduce the risk of irritation of the arachnoid and the pia to a minimum, cotton-wool impregnated with paraffin wax was employed to form the tumours and the tumours themselves were placed outside the dura. It has been pointed out that an examination of the cerebrospinal fluid never provided evidence of a pleocytosis, although there was occasionally a slight increase in total protein content. Indian ink introduced into the cisterna magna spread to the very margin of the tumour and occasionally it was observed to enter the subarachnoid space immediatelv underlying it. A careful histological examination of the brains failed to detect evidence of an inflammatory lesion and the arachnoid and pia underlying the tumours never presented more than a slight degree of cellular proliferation.

We can, therefore, exclude this possibility with some degree of confidence.

(2) A tumour of a given size which caused, when placed below the tentorium, a marked increase in the pressure of the cerebrospinal fluid, had little or no effect when placed above the level of the tentorium. It is improbable, therefore, that the proportion of the intracranial cavity occupied by the tumour is a determining factor, at all events during the initial stages of the syndrome.

(3) (*a*) No evidence could be obtained that the tumours caused either the great vein of Galen or the straight sinus to be obstructed. It is evident from Fig. 1 that the great vein of Galen is in no way compressed. Experimental evidence [3, 4, 5, 6] has been presented elsewhere which suggests very strongly that venous congestion of the choroid plexuses does not cause any increased production of cerebrospinal fluid.

(*b*) The suggestion that the tumour may cause an increased production of cerebrospinal fluid, in some manner still undetermined, is certainly justifiable in view of our ignorance of the mechanism by which the cerebrospinal fluid is normally produced. No useful purpose will be served, in the entire absence of data, by speculating as to the possible means by which this could be effected.

(4) (*a*) The pressures of the cerebrospinal fluid in the lateral ventricles and in the cisterna magna were always identical. Moreover, pressure changes in the cisterna magna were followed by corresponding changes of pressure in the lateral ventricles, and *vice versa*. A careful examination of brains in which Indian ink had been allowed to circulate for varying periods of time revealed no evidence that the ink had been held up in any particular situation. No demarcation line was ever observed. It must be admitted, however, that although these observations suggest very strongly that there was no complete block to the circulation of the cerebrospinal fluid between the cisterna magna and the base of the brain, they do not exclude the possibility of a partial or an intermittent obstruction in this region. Attention, however, has already been drawn to the fallacies which are attendant on the Indian ink method of investigating the circulation of the cerebrospinal fluid.

(*b*) We have now to consider the possibility that the tumours may have raised the tentorium and caused the cerebral hemispheres to be displaced upwards against the vault of the skull. It is conceivable that this may interfere with the passage of the cerebrospinal fluid over the cerebral cortex and so lead to a diminution of absorption. It is noteworthy that the occurrence of papillœdema with subtentorial tumours in man could perhaps be accounted for on such a basis.

Elsberg and Silbert [12] have shown by means of encephalograms in the human subject that a tumour of one cerebellar hemisphere tends to produce a greater dilatation of the opposite lateral ventricle than of the ventricle of the same side. A unilateral cerebellar tumour or a tumour of the cerebellar-pontine angle often produces distortion of the posterior horn of the homolateral ventricle in an upward, forward and outward direction. Stopford has drawn attention to the possible risk of occlusion of the great vein of Galen as a result of elevation of the tentorium by subtentorial tumours in man.

The presence of Indian ink over the entire cerebral cortex need not be regarded as providing evidence against this view. The highest cerebrospinal fluid pressure encountered in these experiments was 450 mm. of normal saline. Although abnormally high, this pressure is probably far below the maximum, and it is reasonable to presume that a considerable proportion of the cerebrospinal fluid was still being absorbed. It is not surprising, therefore, that the ink was able to spread over the entire cortex in all these experiments. A careful comparison of brains containing tumours with normal brains failed, however, to demonstrate any pronounced elevation of the tentorium. It is, therefore, very doubtful whether the resulting displacement of the cerebral hemispheres would be sufficient to cause any interference with the circulation of the cerebrospinal fluid over the cortex.

On the other hand, it is evident from Fig. 1 that the tumour is tending to displace the cerebellum in a forward direction. This may be accompanied by a displacement of the brain stem and of the cerebral hemispheres in the same direction, which may ultimately lead to an embarrassment of the circulation of the cerebrospinal fluid over the cerebral cortex. Here again, however, it is doubtful whether the hemispheres are displaced to a significant extent. Moreover, experiments on the effect of artificial supratentorial tumours which are now in progress, would seem to provide evidence that the cerebral hemispheres may be displaced to a considerable degree without having any effect on the pressure of the cerebrospinal fluid in the cisterna magna. It is, therefore, very doubtful whether the raised pressure of the cerebrospinal fluid in the experiments under consideration can be accounted for on such a basis.

(*c*) The venous pressure in the torcular was within normal limits in every case of subtentorial tumour which was uncomplicated by venous clotting. Experimental evidence [5, 6] has also been provided that a raised venous pressure in the torcular is compatible with a normal cerebrospinal fluid pressure. It is improbable, therefore, that the raised pressure of the cerebrospinal fluid can be accounted for on this basis.

To sum up, it would appear that the raised pressure of the cerebrospinal fluid in these experiments may have been caused in two possible ways:—

(1) The tumour may have caused an increased production of cerebrospinal fluid in some way still undetermined. The excess of fluid may have been so great that the absorption apparatus was unable to deal with it, or the normal cerebrospinal fluid channels distal to the cisterna magna may have been relatively too small to permit it to circulate freely.

(2) The circulation of the cerebrospinal fluid may have been obstructed at some point between the cisterna magna and the base of the brain. The obstruction was probably incomplete or intermittent in character.

Considerable improvement, however, will be necessary in the means available for investigating the circulation of the cerebrospinal fluid before it is possible to decide with any confidence which view is the correct one.

It is necessary, before concluding, to consider the four cases of hydrocephalus. The experimental findings have already been described in detail. Latent hydrocephalus has been encountered in less than one per cent. of laboratory dogs. The condition was symptomless and was discovered during routine examination. It is, therefore, conceivable, although improbable, that the hydrocephalus was present before the tumours were introduced. Experimental tumours probably produce their maximum effect shortly after introduction. After six days, however, the brain may have accommodated itself partially to the tumour, and local œdema, if present, may have had time to subside. It is conceivable, for example, that an obstruction to the circulation of the cerebrospinal fluid which was complete during the early part of the experiment, would later become partial or intermittent. The pressure of the cerebrospinal fluid may then be no greater than that in cases uncomplicated by hydrocephalus. It is impossible, however, in the absence of essential data, to be certain of the precise origin of the hydrocephalus. Nevertheless, the slight but unmistakable dilatation of the aqueduct and of the fourth ventricle which was present in each case, would seem to suggest that the hydrocephalus had not been caused by a temporary occlusion of these structures.

SUMMARY.

(1) The available literature relating to the origin of the increased pressure of the cerebrospinal fluid associated with intracranial tumours is reviewed.

(2) A method is described by which artificial subtentorial tumours, consisting of cotton wool impregnated with paraffin wax, can be produced in dogs and their effects on the intracranial pressures studied.

(3) Subtentorial tumours were successfully produced in twenty-one dogs. The tumours, with one exception, were extradural in situation. The animals were allowed to survive, on the average, for six days. During the survival period they maintained good health and were symptomless. When examined at the end of this period, the pressure of the cerebrospinal fluid in the cisterna magna was found to be raised. The venous pressure in the torcular and the arterial pressure in the femoral artery were within normal limits.

(4) Hydrocephalus was encountered in four of the animals. The

dilatation was moderate in degree, and involved the lateral and third ventricles, although the aqueduct and the fourth ventricle presented definite evidence of slight dilatation.

(5) Indian ink introduced into the cisterna magna spread over the entire cerebral hemispheres in all animals investigated in this way.

(6) A criticism is presented of the method of investigating the circulation of the cerebrospinal fluid by introducing Indian ink into the cisterna magna.

(7) The possible means by which the tumours may have raised the pressure of the cerebrospinal fluid are discussed.

(8) It is concluded that the experimental findings are compatible with the following mechanisms:—

(*a*) There may have been an increased production of cerebrospinal fluid by the choroid plexuses which was brought about by a mechanism still undetermined. The absorption apparatus may have been unable to deal with the excess of fluid, or the cerebrospinal fluid channels distal to the cisterna magna may have been relatively too small to permit it to circulate freely.

(*b*) Displacement of the brain stem may have led to an obstruction of the circulation of the cerebrospinal fluid at some point between the cisterna magna and the base of the brain. The obstruction was probably incomplete or intermittent in character.

REFERENCES.

[1] Baurmann, M. *Bericht der Deutsch. Ophthal. Gesellsch.*, 1927, **46**, 96.

[2] Becht, F. C. *Amer. Journ. Physiol.*, 1920, **51**, 1.

[3] Bedford, T. H. B. *Brain*, 1934, **57**, 1.

[4] *Idem. Ibid.*, 1934, **57**, 255.

[5] *Idem. Ibid.*, 1935, **58**, 427.

[6] *Idem. Ibid.*, 1936, **59**. 324.

[7] Berens, C., Smith, H. T., and Cornwall, L. H. *Arch. Neurol. and Psych.*, 1928, **20**, 1151

[8] Brain, W. R., and Strauss, E. B. "Recent Advances in Neurology," London, 1934.

[9] Dandy, W. E., and Blackfan, K. D. *Amer. Journ. Dis. Child.*, 1914, **8**, 406.

[10] Dandy, W. E. *Annals of Surgery*, 1919, **70**, 129.

[11] Duke-Elder, W. S. *Journ. Physiol.*, 1926, **61**, 409.

[12] Elsberg, C. A., and Silbert, S. *Arch. Neurol. and Psych.*, 1928, **19**, 596.

[13] Gibbs, F. A. *Ibid.*, 1936, **35**, 292.

[14] Hodgson, J. S. *Journ. Amer. Med. Assoc.*, 1928, **90**, 1524.

[15] Magitot, A. P. *Amer. Journ. Ophthal.*, 1922, **5**, 777.

[16] Masserman, J. H., and Schaller, W. F. *Arch. Neurol. and Psych.*, 1933, **30**, 107.

[17] *Idem. Ibid.*, 1933, **29**, 1222.

[18] Masserman, J. H. *Ibid.*, 1934, **32**, 523.

[19] Paton, L., and Holmes, G. *Brain*, 1911, **33**, 389.

[20] Stopford, J. S. B. *Ibid.*, 1928, **51**, 485.

[21] Weed, L. H., and Hughson, W. *Amer. Journ. Physiol.*, 1921-22, **58**, 101.

OBSERVATIONS ON THE ROENTGEN TREATMENT OF INTRACRANIAL GLIOMATA WITH ESPECIAL REFERENCE TO THE EFFECTS OF IRRADIATION UPON THE SURROUNDING BRAIN.[1]

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ALTHOUGH in recent years there has been considerable interest in the treatment of the gliomata by roentgen radiation, there remain differences of opinion as to its value and as to the most suitable technique in its application. In the following pages the effects of roentgen rays upon normal nervous tissue will be described at some length—both as recorded in the literature and as seen in tissues examined in connection with the present investigation. Then the effects of irradiation upon the various members of the glioma group will be very briefly considered. Finally, from a consideration of the available data, an attempt will be made to arrive at some temporary conclusions on the subject of the dosage of irradiation to be employed in the treatment of these tumours.

(1) THE EFFECT OF IRRADIATION UPON NORMAL NERVOUS TISSUE.

Historical Survey.

Before roentgen therapy can be used successfully in the treatment of any tumour, it is necessary that the cells of the tumour be more sensitive to the irradiation than the cells of the surrounding normal tissues. The greater this difference in the sensitivity of the tissues, of tumour and host, the more likely is the treatment to be beneficial, since an adequate dose can be administered to the tumour without the production of damage in the surrounding tissue. With a view to determining the sensitivity of the brain tissue to irradiation, numerous experimental observations have been made by various workers. In addition, there are a number of reports of symptoms of nervous involvement following irradiation of the scalp for superficial lesions. The literature dealing with this matter will now be considered, and then the results of the examination of a series of brains which had been subjected to intensive irradiation in the treatment of gliomata will be described.

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Lyman, Kupalov and Scholz [16] review the literature on the subject of the effect of roentgen rays on the animal brain. They point out that there is disagreement as to the effects produced in young animals, some authors describing definite parenchymal changes, while others are of the opinion that the only alterations are to be found in the vascular system " or other labile elements." In the case of adult animals there is general agreement that little or no direct effect is produced on the nerve-cells and fibres, although changes may be produced in the blood-vessels and a mesodermal reaction called forth. These authors' work consisted firstly in the investigation of the conditioned reflexes in four dogs whose brains had been subjected to irradiation and secondly in the pathological examination of the brains of these animals. Definite physiological disturbance was observed: for example a diminution of spontaneous activity, a disappearance of conditioned reflexes and later the development of signs of diffuse cerebral damage. Pathologically the authors stress the blood-vessel changes and believe these to be the essential features. They noted especially regressive changes in the capillaries, hyaline and sclerotic changes in the arterioles, and an inflammatory reaction around the blood-vessels. Areas of necrosis were present and diffuse degenerative changes, such as fat in the ganglion cells. Demel [10] confirmed the physiological findings of Brunner and Schwartz [5] by the irradiation of four-day old puppies and produced deficient growth, ataxia and retinal changes, together with small hydrocephalic brains. He quotes Brunner as having found changes in the histologically labile elements, acute hyperemia of the leptomeninges, hæmorrhages and œdema, but no changes in the adult ganglion cells, nerve fibres or glia. Scholz [20, 21] reviews previous work and states that young animals react to high doses of irradiation by cramps, ataxia, paralyses or even death, and that the brain shows hæmorrhages. He points out, however, that adult animals can withstand very high doses, the brain simply showing degenerative changes and proliferative alterations in the blood-vessels. In his own dogs, ataxia, paralyses and stupor occurred in those allowed to survive for a period of twelve months after irradiation. On the other hand, animals killed five weeks after irradiation showed no physiological disturbance. In the latter group the pathological changes noted consisted of lymphocytic infiltration around the smaller blood-vessels in the white matter, together with fibroblastic proliferation. There was some swelling of the astrocytes and occasional rod-cells were seen. The nerve cells were unchanged. The animals killed at a later period showed circumscribed hæmorrhages which the author suggested might be due to capillary injury. The larger blood-vessels showed fibrosis of the adventitia and hyaline transformation in this layer. These latter changes appeared to spread into the surrounding parenchyma. There were no primary changes in the parenchyma, such alterations as were seen in the animals killed after five weeks having disappeared. He notes that none of these changes was found in control animals which had been subjected to similar periods of anæsthesia but had, of course, received no irradiation.

The effect of roentgen irradiation on the production of cerebrospinal fluid is also of interest. In a recent paper which is in accord with the present views on the subject, Skefer [22] states that while small doses diminish the production of cerebrospinal fluid, larger ones at first stimulate its production, but later depress this further. This is of interest in that it suggests that roentgen irradiation may produce a temporary improvement in symptoms in the case of radio-resistant tumours, and thus the therapeutic test is valueless and dangerous.

The observations dealing with the effects of roentgen radiation on the human brain are less numerous. Alpers and Pancoast [1] describe the results of the histological examination of a number of brains which had been subjected to irradiation. The blocks of tissue examined in their cases had been "in close approximation to the tumour" and "under the decompression or bone-flap" through which many of the rays had been directed. The authors observed in these regions a loss of some cortical nerve-cells with an accumulation of fat in others, and also in the capillary endothelium and astrocytes. Since fat appears in the cortical nerve-cells under various conditions, its presence is not attributed to the irradiation, except in the case of the cerebellar Purkinje cells, where none can normally be demonstrated. From a consideration of their findings, the authors believe that much larger doses than hitherto employed by them may in future be used with advantage. It may here be mentioned that such degenerative changes as those described above which occur *in the immediate neighbourhood of the tumour* or *at the site of herniation of the brain through an opening in the skull* may be due, not to the irradiation, but to the tumour itself or the trauma from the margins of the bony defect.

Apart from this work of Alpers and Pancoast, the reports concerning the effects of roentgen irradiation on the nervous parenchyma deal with certain untoward results which have followed such treatment of the scalp for some superficial lesion. Fischer and Holfelder [12] describe the case of a man with a canceroid tumour of the temporal region which was treated by roentgen radiation. Seven years later he began to have attacks in which he became restless, felt hot and was unable to speak, together with numbness and twitching of the left hand and foot. An exploration was carried out in the right fronto-parietal region. The brain was described as being blue and full. There was no evidence of metastasis. A biopsy revealed a localized amyloid change only, and it is suggested that this may have been the result of the irradiation.

Markiewicz [17] records a case in which five years after the first, and one and a half years after the second, of two roentgen irradiations. for a scalp lesion, a man aged 34 became blind and paraplegic and commenced to have epileptic attacks. Later he developed a roentgen ulcer in the occipital region and died after two years of symptoms. Examination of the brain revealed multiple hœmorrhagic necrotic areas, mostly in the cortex and especially in the occipito-parietal region. There were also changes in the cortical and pial vessels, and the author considers that these were primary and gave rise to the parenchymal degeneration. Colloidal masses were found to be widely distributed through the parenchyma. It will be noticed that these changes resemble those which Scholz [20, 21] described as occurring in the irradiated brains of dogs and which have been described above. Lorey and Schaltenbrand [14] record two cases in which it appears that damage to the nervous parenchyma had been caused by roentgen irradiation for scalp lesions. The first of these was that of a 5-year-old girl who was suffering from trichophytosis of the scalp. Treatment by irradiation resulted in complete epilation within a period of three weeks. Three months after this, hair appeared again on the left side of the scalp, but not on the right. One year after the treatment there began to occur epileptic attacks and left-sided weakness was noticed. One year later the child had an acute episode with fever, convulsions and a left hemiparesis. At the age of 12 (seven years after the treatment) the left side of the body was under-developed and, though major attacks were less frequent, there were numerous minor ones. Roentgen examination of the skull revealed changes which appeared to correspond fairly accurately with the atrophic and telangiectatic changes in the right side of the scalp. A well-marked atrophy of the skull and a superficial calcification within the cranial cavity were present. Encephalography revealed that the right lateral ventricle was wider than the left, suggesting an atrophy of the right hemisphere. Because of the correspondence of the skull changes and the roentgen-injured region of the scalp with the neurological disturbance, the authors suggested that the irradiation had injured the scalp, cranium and meninges. It was believed that a dural hematoma had developed in this area. This had injured the cortex and given rise to under-development, epilepsy, and a spastic hemiparesis of the opposite side. Finally the inflammatory products in the meninges had become calcified. In a second paper, Schaltenbrand [24] states that the presumptions in the above case were verified by trephination, a pachymeningitis hæmorrhagica being disclosed. He then describes another somewhat similar case, that of a 21-year-old woman who had received roentgen therapy for a microsporonic infection of the scalp when 9 years of age. During the period of this treatment there had been pyrexia on two occasions, associated with which were some signs of bronchitis. At 15 years of age, after it had been obvious for some time that the child was nervous and emotional, she was brought to the clinic because of delirium, associated with fever. She was found to have an aphasia, deviation of her head and eyes to the left and a right flaccid hemiparesis. There were clonic twitchings of the right arm and face. Gradually her mental state improved, the aphasia and hemiparesis disappeared and the attacks of twitching of the right face and arm became less frequent. Encephalography showed a symmetrical ventricular dilatation. At the age of 21 the patient returned with an increase in the frequency of the epileptic attacks. Most of the hair of the scalp was absent and its skin thin and atrophic. X-ray showed patchy defects in the cranium and in one place some flaky intracranial calcification. The author concludes that the original treatment at the age of 9 injured the cranium and brain and that after a latent period of three years an encephalitis-like illness resulted which gave rise to the right hemiparesis and epileptic attacks.

Summarizing, it will be inferred from these observations that there is both clinical and pathological evidence that roentgen irradiation may produce damage in the tissues of the central nervous system. The histological effects have for the most part been considered secondary to the vascular damage which is the direct result of the irradiation. The nervous parenchyma itself has been considered to be relatively resistent.

Personal Observations.

For the present work, six brains were subjected to the histological examination to be described below. The first, used as a control of our methods, was that of a subject, aged 36, and not afflicted with a brain tumour, who died suddenly while undergoing treatment for a hæmatemesis from a peptic ulcer. Another was that of an older man who died from a brain tumour before any treatment could be given. This brain was examined so that changes produced by the tumour itself might not be wrongly attributed to irradiation in the other brains. The remaining four were the brains of tumour cases which had received large doses of irradiation. In all these cases, blocks of tissue were taken from both the right and left cerebral hemispheres in each of the following regions: (1) Centrum semiovale; (2) prefontal region; (3) striate (occipital) region; (4) temporal region; (5) parietal region; (6) precentral region; and (7) basal ganglia. In addition a block of cerebellar hemisphere was examined in each instance. Each of these blocks was then examined by the following technical methods— Nissl's toluidin blue, Bielschowsky's nerve-fibre method, Cajal's gold-sublimate method for astrocytes, Herxheimer's stain for fat, and Kultschitsky's modification of Weigert's method for myelin sheaths. In a number of instances, Penfield's modification of the Hortega technique for oliogdendroglia and microglia has been used, as also the Van Gieson stain for clearer demonstration of the blood-vessels. The cases will now be considered in detail:—

Case 1.—R. G., Unit No. 141072. Control brain removed from a man, aged 36. In this case it will be of no interest to discuss the clinical history, except to state that the patient died suddenly when responding well to treatment ten days after a large hæmatemesis from a duodenal ulcer. Necropsy was performed six hours post mortem. The histological examination revealed absolutely no abnormality. It is noteworthy, however, that on staining the tissue by Herxheimer's method for lipoid substances, it was found that in a few of the larger cortical neurones there were granules which stained a faint pink, while a few macrophages on the walls of the smaller cortical capillaries reacted in similar fashion. Repeated efforts failed to demonstrate more than this minimal quantity of lipoidal material.

Case 2.—C. Z., aged 51, Unit No. 151482, was admitted to the Billings Hospital, May 15, 1936, complaining of diplopia, headaches, dizziness and mental confusion.

History.—Six weeks previously his illness had commenced with severe frontal headache, more marked on the right side. Shortly afterwards he noted mental confusion and became awkward in using his left hand. Two weeks before admission he began to suffer from dizziness and diplopia.

Examination revealed a somewhat inattentive and confused patient. No papillœdema was present. There was a complete left homonymous hemianopia. The right palpebral fissure was narrower than the left and there was some weakness of convergence. The other cranial nerves were not involved and motor power and co-ordination were apparently not disturbed. Examination of sensation demonstrated only a deficiency in position sense in the left great toe and left fingers. The abdominal reflexes were somewhat diminished on the left. In walking it was noted that the patient dragged his left toes and did not swing his left arm. Laboratory examinations, including serology, were negative. The pineal shadow was demonstrated by X-ray to be slightly displaced to the left.

A diagnosis of right temporo-parietal glioblastoma was made and on May 23 a right temporo-parietal osteoplastic craniotomy was performed under general anasthesia by Dr. Bailey. No tumour was visible on the surface of the brain, but with an exploratory needle a mass was palpated 3 cm. beneath the surface in the upper temporal region. Owing to a sudden fall in blood-pressure and the fact that it was obvious that the tumour could not be excised, it was decided to leave the operation as a decompression preliminary to irradiation. The patient's condition was poor after operation, and he died two days later.

At the necropsy, which was performed two hours after death, a large tumour was disclosed in the right occipito-parietal region. It extended laterally to within 5 mm. of the cortex, posteriorly to within 3 cm. of the occipital pole and anteriorly as far as the postcentral gyrus. On its cut surface numerous yellow, hæmorrhagic and cystic areas were to be seen. Microscopically the tumour had the typical structure of a glioblastoma multiforme.

The examination of the brain for lipochrome pigment revealed that more of this was present than in the previous case, an occurrence to be expected in view of the difference in the age of the patients. The pigment occurred especially in the ganglion cells, where it took the form of fine granules, and in macrophages gathered around cortical and subcortical blood vessels in which it formed coarser granules. No pigment could be demonstrated in the neuroglia of the cortex or white substance. It was noteworthy that the nerve-cells which contained the pigment appeared in all other respects to be normal, there being no displacement of the nucleus or change in the cell-body or its processes. The change was most marked in the temporal cortex on both sides. The nerve-fibre stains revealed no abnormality in the cells or their processes and no abnormality was detected in the astrocytes or myelin-sheaths (except, of course, in the immediate neighbourhood of the tumour where the astrocytes were swollen and their processes broken up, while the myelin sheaths lying between the tumour cells were fragmented). With the Nissl stain, it was found that the tigroid substance was only faintly stained; due doubtless to formalin fixation, but appeared of normal distribution. It will thus be seen that few changes of significance were produced in the brain around this large tumour. The findings in this brain agree very well with those of Caspar in similar cases which will be discussed later.

Case 3.—P. W., aged 45, Unit No. 80234, a carpenter, was admitted to the Billings Hospital, April 6, 1933, complaining of headaches.

History.—The patient had been subject to sick headaches since childhood, but two months before his admission these had become much more severe, radiating forward from the right occipital region. For a similar period he had become aware of a poor memory, blurred vision, dizziness and numbness of his arms and legs. The visual disturbance had been progressive and more marked in the right eye. The attacks of giddiness had come on especially while walking, surrounding objects appearing to whirl and the patient falling forward. There had been an attack of nausea and vomiting prior to the onset of the other symptoms, but this had not recurred.

Examination.—The patient was mentally slow, but otherwise normal and co-operative. There was tenderness on percussion of the right parietal region of the skull and a resistance to flexion of the neck. Visual acuity was markedly diminished (more so on the right) and both fields, especially the right, were grossly constricted. There was bilateral papilloedema, 4 to 5D on the right and 2 to 3D on the left with small retinal arteries and tortuous veins. There was a slight degree of exophthalmos on the right, and the left pupil was larger than the right, both having normal reactions. There was slight bilateral limitation of lateral gaze and a diplopia on looking to the right. There was also a slight weakness on the left lower face. No abnormality was detected in the motor or sensory system and the reflexes were normal. The gait was a little unsteady but Romberg's sign negative. Laboratory examination, including serology, revealed no abnormality and X-ray of the skull demonstrated no sellar change, pineal shift, or convolutional markings. Ventriculogram on April 13 revealed that the left ventricle was displaced to the left and not filled in its central portion. No filling of the right lateral ventricle was seen.

On April 15 a right frontal osteoplastic craniotomy under ether anæsthesia was performed by Dr. Bailey and revealed an extensive glioma of the right hemisphere with a reddish grey surface-extension in the right frontal region. A portion was removed for histological examination, a decompression made and the wound closed. Histologically the tumour proved to be a cellular glioma, probably to be classified as a protoplasmic astrocytoma, but showing evidences of malignancy in the number of multinucleated cells and the general polymorphism. Following his recovery from operation and between the dates of April 24 and September 12, 1933, he received 12,645 r. units of irradiation (measured in air). The dose was administered through multiple portals. Transitory erythema of the scalp and permanent epilation occurred.

The patient felt well and returned to work. He was seen from time to time and his decompression remained soft until three years later, in March, 1936, when it was noticed at home that he had "lost interest in things." A left hemiparesis gradually appeared and the decompression became tense. He was given 630 r. additional irradiation, but gradually passed into coma on April 24, and died three days later.

A post-mortem examination was performed eleven and a half hours after death, but the brain had been fixed some hours previously by arterial injection. It revealed flattening of the convolutions of the cerebral hemispheres which was most marked in the right frontal region, this frontal lobe being at least a quarter larger than that of the opposite side. On section the right frontal lobe contained a large tumour mass which extended posteriorly as far as the central region. Histologically the tumour was more cellular and of somewhat more malignant type than that obtained at the biopsy three years previously (Plate XI, fig. 5).

There was a definite and generalized increase in what may be termed lipochrome substance in this brain. It affected not only the nerve cells, but also the walls of the blood-vessels, the macrophages and the neuroglia. The cortical neurones were for the most part uniformly affected and on many occasions the discrete granules of lipochrome pigment, which are seen here normally in later life, had condensed to form a mass which had displaced the nucleus toward the periphery of the cell. In the Purkinje cells of the cerebellum, in which this substance is usually not found, it was abundant and was clearly demonstrable also in the neighbouring basket cells. Around many nuclei, which were obviously those of glia cells in the cortex, there were similar granules of this lipoid material. On the walls of the cortical capillaries the adventitial cells were very frequently seen to be loaded with it (Plate IX, fig. 2) and grouped around the larger cortical and subcortical vessels were macrophages similarly laden. It is to be noted that in the subcortical regions the substance was found only around the blood-vessels, where it was contained in macrophages. The tumour cells also contained this material in large globules.

In the sections impregnated by the Bielschowsky method the changes produced were not as generalized and, excluding those in the right frontal region (the site of the tumour), were most marked and equally so in the temporal cortex of both sides and the left precentral region. In these regions, especially, the nuclei of the nerve cells were eccentric in many cases and the cytoplasm, including that of the apical dendrites, vacuolated with destruction of the neuro-fibrillæ. In Plate IX, fig. 1, is seen a nerve cell, showing these changes. They are no doubt to be associated with the accumulation of excessive amounts of lipochrome substance. In addition to these well-marked changes, it was noted that throughout the brain the neurofibrillæ were not well impregnated. Except in the region infiltrated by tumour, the nerve fibres in the white matter showed no abnormality.

In the Nissl preparations there was noted an almost complete failure to stain the tigroid substance in the cerebral cortical cells, although the technique had been successful in the case of the cerebellar Purkinje cells. Also in both right and left temporal regions and the left prefrontal region (which had shown the most marked changes in the Bielschowsky preparations) well-marked satellitosis and neuronophagia were to be seen in the Nissl specimens. In the preparations to demonstrate astrocytes, the changes were not remarkable. In the temporal regions on both sides there was some clasmatodendrosis and in other regions, where this advanced change was not found, the astrocytes were often found to have enlarged cell bodies and somewhat irregular processes. In neither Nissl nor van Giesen preparations were any changes demonstrable in the blood-vessels which, therefore, departed from the normal only in having their sheaths infiltrated with the fat-laden macrophages. Except in the region of the tumour, there was no demonstrable change in the myelin sheaths of the nerve-fibres—neither in the tangential nor vertical fibres of the cortex, nor in the subcortex.

To sum up, it may be said that in this brain definite degenerative changes were found. They affected the nerve-cells and, to a less extent, the neuroglia. The blood-vessels were for the most part unaffected. There was no evidence of any mesodermal reaction, though fat-laden macrophages were to be found around most of the small vessels.

Case 4.—E. W., aged 32, Unit No. 77948, unemployed, was admitted to the Billings Hospital on March 26, 1933, complaining of convulsive seizures associated with loss of consciousness which had been occurring for the previous ten weeks.

History.—Two and a half months previously the patient had begun to have attacks in which his arms underwent rhythmical jerking movements, both equally. On one occasion this was associated with loss of consciousness and he believed that he had then remained unconscious for fifteen minutes. Since this attack he had been aware of a constant buzzing noise in his left ear, and at times had noticed a transient unpleasant odour without any obvious cause for it. In addition, throughout the period of his illness his memory had been poor and at times he had had difficulty in naming familiar objects. Since the onset of his other symptoms he had also suffered from a left parietal headache radiating at times to the back of his neck. There had been no vomiting and no visual disturbance. Neither was there any weakness of the limbs, nor sensory disturbance. However, he believed, that his gait had been uncertain.

Examination revealed a well-oriented man who appeared to cerebrate slowly. There was a slight difficulty in expression and in writing certain characters. There was tenderness on percussion of the skull in the left temporo-parietal region and a left hyposmia. Vision was normal as were the ocular fundi, but the visual fields showed a slight defect in the right lower temporal quadrants. The left pupil was slightly larger than the right, and there was a suggestion of hypæsthesia in the area of distribution of the left trigeminal nerve, together with slight weakness of the left masticatory muscles. Further examination of the motor and sensory systems revealed no abnormality and the reflexes were also normal, except that the left abdominal and left cremasteric reflexes appeared to be diminished. The patient's station and gait were undisturbed. Laboratory investigation, including serology, revealed no abnormality and X-ray examination showed a normal skull. A diagnosis of left temporal glioblastoma was made and on March 28, 1933, Dr. Bailey turned down a left temporo-parietal osteoplastic flap and on incision of the cortex in the region of the junction of temporo-parietal and occipital lobes, came upon grey avascular tumour tissue, at a depth of 1 cm. A biopsy was made, a large decompression left and the wound closed without any attempt at excision of the tumour mass. Histological examination of the tissue revealed that it was a protoplasmic astrocytoma showing some cellular polymorphism and multinucleated cells. It was thought that in addition there might be some participation of oligodendroglia in the growth, though this was not proved by specific impregnation.

Roentgen therapy was commenced immediately and between April 7 and August 18, 1933, 8,178 r. units (measured in air) were administered through multiple portals while between May 29 and July 5,1934, a dose of 7,250 r. units was given. Thus in a period of just over a year a dose of 15,500 r. had been administered, the first half of this over a four months' period and the second in the much shorter space of six weeks. There resulted a severe dermatitis of the scalp with much weeping. Following this treatment the patient's attacks continued, though at longer intervals, and apart from this he was at first considerably improved. Later, however, he lost his appetite and complained of weakness, listlessness and loss of energy. The decompression remained soft and flat. On April 12 vomiting appeared, together with numbness of the left arm and leg. There was drowsiness, which passed later into coma and the patient died on January 26, 1935. It is of interest to note that at no period did the decompression become tense or bulge.

A necropsy was performed two and three-quarter hours after death and the brain was immediately sectioned, blocks being placed in Zenker's fluid, formalin, formalin-bromide and alcohol. There was found in the left hemisphere a large mass of abnormal tissue extending from the anterior portion of the left temporal lobe to within 2 cm. of the occipital pole. It had one cystic cavity 2 cm. in diameter at its centre and there were numerous surrounding cysts. There was considerable œdema of this hemisphere. Histological examination of several regions in the mass revealed extensive degeneration with some areas of marked astrocytic proliferation—undoubtedly tumour (Plate XI, fig. 6)—and no evidence of malignant transformation.

The results of the examination of the surrounding brain by the various histological methods will now be described. In the material stained by Herxheimer's method, a very large amount of lipochrome substance was demonstrated throughout the brain. This was present in greatest amount in the cortex, where it occupied not only the nerve-cells but was clearly evident in the oligodendroglia and in the astrocytes of the first layer of the cortex beneath the pia mater. A large quantity of the material was deposited in the adventitial cells of the cortical capillaries (as in Plate IX, fig. 2), while in the white matter there were numerous fat-laden macrophages around the blood vessels. The changes were widespread and marked, but on the whole it seemed that there was more of this material demonstrated in the nerve-cells of the right temporal cortex than in those of any other region. In the Bielschowsky preparations, the displacement of the nucleus and vacuolation of the cells with destruction of neuro-fibrillæ, which have above been associated with excess of lipochrome substance, were again clearly seen (as in Plate IX, fig. 1). As was the case in the Herxheimer preparations, these changes were widespread. It was noticed, however, that the cells in the occipital region of both hemispheres were less affected than elsewhere.

In the Nissl preparations many changes were discovered, and may with benefit be classified into three groups according to whether the nerve-cells, the glia or the vascular tissues are involved. Many of the nerve-cells were found to have heavily stained nuclei and swollen bodies; satellitosis and neuronophagia were widespread. In one small cortical area there was noted an entire absence of nerve-cells and a commencing glial scar (Plate X, fig. 1). The most striking change in the glia was an increase in the cortical, and especially the subcortical astrocytes, many of which were of the swollen type, described above. There were areas in which groups of these large astrocytes were found, the "gliarazen" of German authors. These differ from glial scars in that the nuclei of the astrocytes are separated by cytoplasm and not by a network of fibrils. There were regions in which proliferation of the glia along the blood-vessels was clearly seen—the so-called "glia walls" (Plate X, fig. 4). There appeared to be a proliferation of the microglia, and numerous swollen oligodendroglia were also noted. The changes affecting the vascular system were also numerous. In the white matter there was well marked perivascular infiltration with lymphocytes, plasma cells and macrophages, many of the latter containing the green granules characteristic of altered blood pigment when stained by this method. Numerous small softenings filled with macrophages were encountered (Plate X, fig. 2). Some adventitial thickening of the blood-vessels was also seen and occasional arteriolar-sclerosis.

Specimens prepared by the Cajal gold-sublimate technique demonstrated scattered changes in the astrocytes, but the changes were not uniform and many astrocytes were entirely normal. However, large swollen astrocytes were commonly seen (Plate IX, fig. 7), and in some regions this change had progressed to a breaking up of the processes which had become reduced to aurophilic granules. In Plate IX, fig. 6, a typical example of this clasmatodendrosis is to be seen.

Because of the changes noticed in the microglia and oligodendroglia in the Nissl preparations, sections from the series of blocks were impregnated by Penfield's modification of Hortega's technique for demonstration of these cells. In this way, widely distributed hypertrophied microglial cells were demonstrated. Some took the form of the so-called "rod cells" (Plate IX, fig. 4), while others had become almost amœboid. In the left temporal region many large phagocytes were seen, and it seemed possible that they represented a further change in the hypertrophied microglia, so numerous elsewhere. Swollen oligodendroglia cells (to which little importance is attached) were also conspicuous in these preparations. No changes were observed in the myelin sheaths.

It will be seen that in this brain, which had received larger doses of irradiation than the previous one, much more pronounced degenerative changes were present. These affected not only the nerve-cells, but also the astrocytes, microglia and possibly oligodendroglia. The blood-vessels were involved to a slight extent only. The clasmatodendrosis and myelin destruction of the temporal lobe might be accounted for by the presence of the tumour, also the proliferative changes in the neuroglia, but certainly not the widespread degenerative changes affecting all parts of the cortex.

Case 5.—J. C., aged 4 years, Unit No. 70249 This example of a medulloblastoma cerebelli will later be briefly considered from the clinical point of view (p. 243). At present the changes found post-mortem in the irradiated brain will be considered.

Specimens prepared by Herxheimer's method revealed a large quantity of lipochrome substance in the cortical nerve-cells and this at an age when there is normally little to be found. In addition, fat in the astrocytes, including those of the first layer of the cortex, was seen and everywhere large microglial cells with their processes laden with fat-granules (Plate IX, fig. 3). In the Bielschowsky preparations there was vacuolation of the nerve-cells with displacement of their nuclei and disappearance of their neurofibrillæ (as in Plate IX, fig. 1). Certain of these cells were seen to be greatly shrunken. The Nissl preparations showed very widespread degeneration of the cortical nerve-cells. Some of these cells were swollen, with their nuclei displaced toward the periphery and the tigroid substance undergoing chromatolysis. Others were shrunken, with nuclei staining very heavily. In addition, in these preparations, large vacuolated neuroglial cells could be discerned as well as numerous large microglia ("rod cells").

The preparations to demonstrate neuroglia showed widespread swelling of the astrocytes with breaking up of their processes (clasmatodendrosis). The Penfield preparations revealed swollen oligodendroglia, but the numerous large microglia seen in the Nissl preparations were not satisfactorily impregnated. Definite changes in the structure of the vessels themselves were frequently observed. Of these the so-called arteriolar sclerosis was most obvious, with its separation of the intima from the adventitia by a wide hyaline zone. Other vessels showed either intimal proliferation with endothelial cells projecting into the vascular lumen, or an adventitial hypertrophy.

It will thus be seen that widespread changes of a type similar to those already described were present in this brain also. They affected the nerve-cells, neuroglia, microglia and even the blood-vessels. The nerve-cells showed more definite evidence of degenerative changes here than in any other case, no doubt due to the age of the patient.

We have examined also the brain of another child (C. S.), aged 5½ years, Unit No. 89864, who received altogether a dose of 14,229 r. units from September 26, 1933, to May 7, 1934, for a cerebellar medulloblastoma, but who died less than a month after completion of the irradiation. The changes in this brain may be briefly summarized by saying that they resembled those found in the brain of Case 3, the nerve-cells being mainly affected. These were swollen and vacuolated, their nuclei being displaced and heavily stained.

(2) THE EFFECT OF IRRADIATION UPON TUMOUR TISSUE.

Bailey, in 1925, suggested that the varying effects of roentgen irradiation upon the gliomata might be due to histological differences within this group of tumours. Following the classification of these tumours by him, it has come to be recognized that the various members of the group differ not only in their gross and microscopical structure, life history and sites of predilection, but also in their response to treatment, whether surgical or radiological. The sensitivity of these different types to roentgen therapy will now be very briefly considered.

Undoubtedly the medulloblastoma is the most sensitive to irradiation of the gliomata. In 1928 Bailey, Sosman and van Dessel [3] reported eleven cases so treated with the average survival period of thirty-nine months, a considerable improvement on the average survival period in non-irradiated cases, which is usually less than twelve months. These authors also pointed out that since the tumour spreads by seeding itself throughout the subarachnoid space, adequate treatment must involve irradiation of the whole central nervous axis. Bailey [2] has described the regressive histological changes occurring in this tumour following roentgen therapy. Other writers have confirmed the above work (e.g. [1, 8]), and many of the cases treated in this clinic have benefited considerably.

As an example may be quoted a boy, aged 4 years (Case 5—above), who was admitted to the Billings Hospital in October, 1932, because of unsteadiness of gait, having had symptoms for six months. A diagnosis of tumour of the vermis was confirmed at operation, when a typical medulloblastoma was disclosed. A biopsy only was carried out. Irradiation caused his symptoms to disappear, and later had the same effect on lumbar pain which appeared in April, 1933, and again in March, 1934. Later, however, irradiation proved unavailing, and the child died in February, 1935. This child had received 13,789 r. units between November 11, 1932, and April 17, 1934. The irradiation in this and the previous cases was delivered at 200 k.v. and 25 m.a.; filtration 1 to 1·25 mm. Cu. plus 1 mm. Al.; intensity about 38 to 42 r. per minute; F.S.D. 50 to 60 cm.; 200 to 300 r. per sitting continuously or in series with varying rest periods. Post-mortem examination revealed that the tumour had spread widely through the subarachnoid space. In Plate XI, figs. 1 and 2, the tumour tissue as it appeared before and after irradiation is seen. Rarefaction has occurred, there is an increase in the collagenous stroma and the nuclei are small and pyknotic in the post-irradiation specimen.

In attempting to assess the sensitivity of the glioblastoma multiforme one is faced with a problem of greater difficulty. The unirradiated tumour so often shows numerous areas of degeneration, hæmorrhage and considerable variations in histological picture in its different parts that it becomes very difficult to attribute any changes observed in irradiated specimens to the irradiation. Thus while some have described structural alterations in this tumour type and believe them to be due to irradiation [1, 9, &c.] the authors feel that the best evidence of its radiosensitivity will be clinical. In the literature no reports of considerable clinical improvement following irradiation of the glioblastoma multiforme have been found and the same holds true for the patients treated in this clinic. An exception, however, will now be described.

S. S., aged 42, Unit No. 91886, unemployed, was admitted to the Billings Hospital on October 13, 1933, complaining of convulsions, right-sided weakness and difficulty in expressing himself.

History.—Four years previously, he awoke one night, felt unaccountably anxious and suddenly became unconscious. He remained so for five minutes. Then he got up and walked around only to become unconscious again, when he returned to bed. The coma persisted for twenty-four hours, during which time he had a number of generalized convulsions. Two and a half years before admission, he began to have convulsions every three to five months. These were right-sided and associated with loss of consciousness, lasting about thirty seconds. There was an aura of stiffness of the right thumb and he believed that he could abort the attacks by hyperextending this thumb. During these two and a half years there had been a progressive increase in weakness of the right limbs, and the patient noticed an increasing difficulty in expressing himself. Headache was rare. No nausea or vomiting was present. There was no visual disturbance.

Examination revealed an intelligent and co-operative patient who had difficulty in naming common objects. There was no tenderness on percussion of the skull and movements of the neck were full and painless. Vision was normal and there was no papillœdema, although the retinal veins were engorged. There was a paresis of the right lower face. The motor system showed a right spastic hemiparesis. There was no sensory disturbance. The tendon reflexes were hyperactive on the right, the abdominal reflexes were absent on this side, but the plantar responses were normal. Examination of station and gait revealed that the patient was unsteady when standing on the right leg and that he did not swing his right arm in walking. Laboratory examinations, including serology, were negative. X-ray revealed a midline pineal shadow and a normal sella turcica.

A diagnosis of tumour in the left central region was made, and on October 24, 1933, a left frontoparietal osteoplastic craniotomy was carried out by Dr. Bucy under local anæsthesia. A firm area measuring 2 cm. in diameter, with dilated pial vessels overlying it, was palpated in the posterior extremity of the second frontal convolution. Elsewhere the convolutions were slightly flattened. The area of the precentral gyrus for the thumb and fingers was localized immediately posterior to the tumour by faradic stimulation. A biopsy only was performed (because of the site of the tumour), and the tissue was reported by Dr. Bailey to be from a glio-blastoma multiforme. A subtemporal decompression was made and the wound closed.

Post-operatively there was an expressive aphasia which rapidly improved, and on his discharge following roentgen therapy, the patient felt well, complaining only of slight difficulty in speech and a little right-sided weakness. Following a course of therapy in which he received 6,068 r. units between the dates of November 3 and December 20, 1933, through a single portal of diameter 10 cm. situated over the tumour, he lost all symptoms, apart from some slowness of speech. There was a permanent epilation of the irradiated area and a transitory exfoliative dermatitis. Since then he has had no convulsions and his decompression is flat. When last heard from on January 8, 1936, he was in excellent condition; he has since moved to another city and to an unknown address.

This would appear to be an example of a malignant glioma, so situated that any increase in size would be at once reflected in the patient's symptomatology. The tumour reacted so favourably to treatment that the patient remains symptom-free after more than fifty months. We have never had any other experience so encouraging with this type of glioma. It is realized that there are certain features in the case unusual in a glioblastoma. The pre-operative history is long, but this is not uncommon when the first symptom is convulsions. The histological picture also is not entirely characteristic, but the tumour is definitely of malignant type with numerous mitoses and the favourable effect of roentgen-therapy upon it is an encouragement to treat such cases in a thorough manner. In this case the situation of the tumour was such that intensive irradiation could be administered directly over the growth through a decompression.

On theoretical grounds one would not expect gliomata composed of more mature types of cell (e.g. fibrillary astrocytoma and ependymoma) to be influenced by irradiation to any marked extent. In this clinic specimens of pre- and post-irradiation tissue are often indistinguishable. Again, in most cases it is impossible to point to clinical improvement as being the result of irradiation, since the tumours are of slow growth, and the patient may live for many years after a partial excision and decompression, without irradiation. The following case may perhaps be considered evidence of the resistance of the fibrillary astrocytoma to irradiation.

A child, aged 4 years, was admitted to the Billings Hospital in December 1932, with symptoms and signs which led to a diagnosis of a left-sided cerebellar tumour. Exploration revealed a solid astrocytoma of the left hemisphere, and as the child's general condition was poor no attempt at excision was made, and a biopsy only carried out. Subsequently a dose of Roentgen radiation, totalling 9,154 r., was administered. As a result of recurrence of symptoms the posterior fossa was re-explored in May, 1935, when a huge solid tumour was again encountered. In this case it was hoped that intensive irradiation might bring about the cystic degeneration so common in cerebellar astrocytomata, but no such change occurred, a fact which lends support to the belief that the more mature types of glioma are resistant to the therapy.

In spite of this, there would seem to be a definite indication for following surgical treatment of some of these benign types of glioma with roentgen irradiation. This indication is the knowledge that these tumours may undergo what might be described as malignant degeneration, Globus [13] has reported a series of five cases in which he states this change had occurred, and Müller [18] describes three similar cases. Bailey, Sosman and van Dessel [3] also believe that such a change may occur, especially in protoplasmic astrocytomata and oligodendrogliomata, and for that reason suggest that operative treatment of these should be followed by irradiation. It has often been recorded that a slowly-growing glioma, present for several years and producing few symptoms, grows rapidly after partial excision and decompression, and quickly produces severe symptoms. Moreover, in benign gliomata, undisturbed by operation; foci with a more malignant appearance may sometimes be found. In Plate XI are photomicrographs of tumour tissue. In fig. 3 is seen the structure of the greater part of a tumour mass (a protoplasmic astrocytoma), while in fig. 4 is seen the structure of a small central nodule in which are to be found numerous mitoses and the cells present the arrangement so characteristic of glioblastoma multiforme. This tumour was found at post-mortem in the frontal lobe of the brain of a man (W. M.), aged 27, who had a history of headaches and failing memory for four months and who died before any treatment could be given him. This young man had long had behaviour difficulties and his academic work had constantly deteriorated to the distress of his father, who had wished him to become a physician. There is every reason to suppose, therefore, that the tumour had been present for some years. It is obvious, of course, that before a tumour can be finally proved to have undergone this de-differentiation, a thorough examination of a number of blocks taken from its various parts should have been carried out at the time of the original operation. This is usually impossible, and the data will remain inconclusive. It should not be necessary to remark that, should the tumour be completely removed at the first operation, subsequent irradiation cannot be credited with the cure. This seems to have happened in the case of certain hæmangioblastomata reported by Sachs, Ruberstein and Arnisen [19]. These authors definitely state that the tumours were removed, often with considerable surrounding brain. The bed of the tumour was then irradiated and the surprising conclusion is drawn that the hæmangioblastomata are very favourably influenced by irradiation. Thus, since it is believed that evidence is now available to show that the more malignant gliomata can be at least retarded in their growth by roentgen therapy, it would seem rational to irradiate also those types which are believed to undergo malignant transformation ; particularly the protoplasmic astrocytoma and oligodendroglioma.

DISCUSSION.

In this paper there has been described a number of changes occurring in brains which were irradiated in the treatment of gliomata. The possibility of these changes being of post-mortem origin may be immediately dismissed. The longest interval between death and the removal of the brain was fifteen hours. Most pathological studies on the Continent are done on brains which are at least twenty-four hours post mortem, since they cannot be removed earlier. The changes such as we describe are not found in such brains. Some of our material was obtained within three hours after death and immediately fixed in optimal fixatives. But before concluding that these changes are the result of the irradiation, it is important that those which may result from the presence of gliomata should be clearly distinguished. Stern [23] has described at length the changes which may be found in brains which harbour tumours. In connection with the nerve-cells, he remarks that no severe "cell sickness" is ever seen. "Chronic cell change" is not infrequent, and he also records that there is frequently an absence of intracellular neurofibrillæ, though these are clearly demonstrable in the dendritic processes. Rarely is any pathological amount of fat demonstrable in the ganglion cells or in the adventitial sheaths of the blood-vessels. As regards the glia, apart from gliosis immediately around the tumour, no remarkable changes are seen ; this being especially true of the glia in the cortex. This author believes that there is sometimes an overgrowth of fibrillary neuroglia, and quotes Alzheimer's finding of amœboid glia in the immediate neighbourhood of a tumour. There is never any perivascular infiltration with plasma cells and lymphocytes and the increase in the number of blood-vessels recorded by Reichert was not found. Such high grade changes as diminution in the number of tangential medullated fibres in the cortex, reported by Raymond and others, were never found, except in the brain hernia through a palliative trephination. The author concludes his review by stating that there is great variation in the picture from case to case, and in many instances no change whatever is to be found. The work of Caspar [7] (confirmed by Biondi [4]) dealing with the same subject may now be briefly reviewed. He states that grossly there is always swelling of the brain around a tumour. This, in some cases, is so extensive as to involve an entire hemisphere. The most characteristic histological change is a rarefaction of the brain tissue which involves especially the white matter and the first layer of the cortex, so that these may have a loose and almost lace-like texture. There is a widespread dilatation of surrounding blood-vessels, which he regards as the cause of the swelling, and in some cases a capillary fibrosis. The nerve-cells themselves show little change, though there may be some falling out of those in the third layer of the cortex, together with an increase in satellitosis. Turning to a consideration of the glia, Caspar notes that there is no change in the white matter, but in the cortex there are found swelling of the astrocytes and clasmatodendrosis. While there is no hyperplasia of these elements, there appears to be an increase in the fibres in the first layer of the cortex and in the subependymal region. He stresses particularly the fact that in undifferentiated gliomas there is complete absence of any reactive change in the surrounding glia. The same is true for the brain in relation to extra-cerebral tumours (e.g. meningiomas), and the author believes that when proliferation of glia is seen at the margin of one of the more differentiated gliomata the apparent change is a part of the tumour, not a reaction to its presence. He finds no change in the oligodendroglia and microglia, and there is rarely any accumulation of macrophages at the margin of the tumour. These various changes are for the most part seen close to the tumour, but in some cases extended for several centrimetres beyond its immediate neighbourhood. Their presence at once makes it obvious that in deciding whether or not roentgen radiation has produced changes in the brain tissue, it is necessary to examine tissue which lies at a considerable distance from the tumour. The findings in our Case 2 above agree in general with those of Caspar. In our experience, proliferative changes in the neuroglia may be widespread in brains harbouring astrocytomas and in the oligodendroglia of brains harbouring oligodendrogliomas, but no general changes occur with glioblastoma multiforme or medulloblastoma.

The changes described in the irradiated brains examined in connection with this work were controlled against both a brain which did not contain a tumour and one which did, but in which the patient had received no treatment by roentgen irradiation. No changes in any way comparable with those found in the irradiated brains were demonstrated in these two cases, and none of similar type has been described in the literature. As further evidence that the changes described in the irradiated brains had been produced by the irradiation, it may be pointed out that of the first two of these (Cases 3 and 4) both had large tumours which had compressed the surrounding brain over a relatively long period. Yet, as has been described, by far the most marked histological changes were found in the brain which had harboured the tumour for the shorter time, but which had received a considerably heavier dosage of irradiation. Again, in the cases of the two examples of medulloblastoma described above, in which one brain showed gross and the other relatively slight changes, after both had been subjected to heavy doses of irradiation, the case showing the greater changes had lived nearly a year after the completion of the irradiation, whereas the other child died within a month. Other clinical observations, for example those of Schaltenbrand, indicate that the time which has elapsed after the irradiation may be an important factor in the production of degenerative changes. Individual variations of sensitivity to irradiation must also play a role as with other tissues. The alterations observed may now be reviewed. None which could be definitely attributed to the irradiation were noted in the leptomeninges. Such appearances as thickening and fibrosis were often demonstrable, but would seem to be explained by the healing of areas traumatized at operation. In the cerebral cortex, and to a less extent in that of the cerebellum, structural alterations were numerous. The nerve-cells showed various retrogressive changes. In many the cell body was swollen and rounded, with the nucleus displaced towards the periphery. Examination of these cells by suitable methods revealed a great excess of lipochrome pigment, often aggregated into large masses, and this material appeared to displace and even destroy the neurofibrillæ. Other nerve-cells were shrunken with darkly staining nuclei, and cytoplasm and irregular processes. No abnormality could be made out in either myelinated or non-myelinated nerve-fibres, except when they were obviously directly involved in the tumour growth. These changes varied from case to case, being mild in one (Case 3), extremely marked in others (Cases 4 and 5), and in general, most severe in the cases which had received the heaviest dosage provided a sufficient time had elapsed after irradiation.

Turning to the interstitial tissues of the cortex, it was noted that the protoplasmic astrocytes impregnated more easily than normally and were often hypertrophied, while the fibrillary astrocytes (in the first layer and immediate subcortical region) were often greatly hypertrophied with swollen bodies. In some areas clasmatodendrosis was well marked. The presence of lipochrome substance in these cells was also frequently observed. Swelling of the oligodendroglia and lipochrome substance within these cells was common, as was marked hypertrophy of the microglia with the formation of rod cells and even perhaps macrophages. Many of the microglial cells contained quantities of lipochrome pigment, and their numbers appeared increased. In the cortical capillaries the adventitial cells were often found to be loaded with lipochrome substance. Surrounding the large blood-vessels were numbers of macrophages containing this substance. These cells gave the impression of being in the process of migration from the surrounding tissues to the blood-vessels. In the cortex in one Case (4) there were found areas of glial scar-formation with an absence of nerve-cells and also small areas of necrosis filled with macrophages.

In the white matter of the hemispheres, no abnormality was observed in the nerve-fibres, but the interstitial tissues showed changes similar to those outlined above. Of these, the changes in the astrocytes were often marked and evidence of glial overgrowth was seen in the "glia walls" and "cytoplasmic glia" above described. In one brain well-marked changes in the vascular system were observed in both cortex and medulla. Perivascular lymphocytic infiltration, arteriolar hypertrophy, with hyalinization of the media and swelling of the intimal coat, and vast numbers of macrophages full of lipochrome pigment in the walls of and gathered around the vessels, were all seen. However, it should be pointed out that in the remaining cases no vascular reaction other than slight medial thickening was seen and it therefore seems certain that in none was the vascular change primary or the factor responsible for the alterations in the nervous tissue itself. This is especially important in the case of medulloblastomata. Here in the terminal stages the leptomeninges were widely infiltrated and it might be expected that vascular obstruction would play a rôle in the production of degenerative changes in the nervous parenchyma. But we have made examination of non-irradiated cases (not herein reported) and no such changes are found in them.

The evidence that roentgen irradiation can injure the normal nervous tissues when administered in therapeutic doses is, however, not entirely histological. Cases from the literature have been quoted above in which, in both man and the lower animals, physiological disturbances have followed irradiation. In some of the human cases, it would seem that the disturbance has been brought about by a considerably smaller dosage of irradiation than is often employed in the treatment of the gliomata. In the patients of this series who were treated by irradiation the clinical evidence of resulting intracranial disturbance was of two types. In the first place, there frequently occurred the well recognized immediate reaction to the therapy which is characterized by drowsiness and even coma, with vomiting, and diminished pulse and respiration rates. This is almost certainly due to a sudden rise in intracranial pressure, which is probably brought about by congestion and œdema in and around the tumour, if not throughout the brain [15]. In the second place, certain of the cases which terminated fatally after roentgen therapy did so without exhibiting the signs of raised intracranial tension which are almost invariably seen as death approaches in cases which have not received such therapy. In these cases the decompression has remained soft and even flat or sunken. Such patients become listless, anorexic and anæmic. They gradually fail and finally die in a cachectic state.

This was the case with R. H., aged 36, Unit No. 84923. A cerebral exploration in the right temporal region was performed in June, 1933, and a soft vascular subcortical glioma found. A biopsy was made and a decompression left over the tumour. The tumour proved microscopically to be glioblastoma multiforme. He received between July and November, 1933, through multiple portals, 4,615 r. Again, from April to July, 1934, he received 2,830 r. The result was complete and permanent epilation of the scalp but only transitory erythema. He was very well and working until January, 1935, when he began to complain of headache and general weakness. Between May and July, 1935, he was given 2,280 r. additional radiation, but he steadily declined and died August 30, 1935. The decompression was never at any time tense although slightly bulging. Necropsy was refused.

It is suggested that in such cases, the roentgen therapy may have been a factor in bringing about a fatal result, although further study would be necessary before such a statement could be made with assurance. It might be noted here that the child C. S. (p. 242 above), who received a dose of 14,229 r. over the cranium and 6,228 r. over the spinal column in the relatively short period of seven months declined rapidly and died some eight months after his operation, whereas similar children treated more conservatively live thirty-six to forty months on the average.

From an examination of the available evidence, both that presented in the literature and in the investigation carried out in connection with this work, it is considered that roentgen irradiation of intracranial gliomata is a therapeutic method of established value. Although it is generally agreed that the medulloblastoma—one of the most undifferentiated of these tumours—is extremely sensitive to irradiation, nevertheless after several treatments it usually becomes resistant and its growth can no longer be restrained. However, symptoms may be relieved and the fatal issue postponed for a considerable period in certain cases. The histological picture of irradiated medulloblastomata also demonstrates their sensitivity to this treatment.

It is believed that another of the more rapidly growing gliomata, the glioblastoma multiforme, is sensitive to irradiation though less so than the medulloblastoma. The clinical record of what is believed to be one example of this tumour has been briefly presented and seems to indicate a complete arrest of the development of the lesion after more than fifty months. While some have attempted to ascribe to irradiation certain retrogressive histological changes in glioblastomata which have received roentgen therapy, we believe that such descriptions are of doubtful value. The histological features so often differ from one part of the tumour to another that it seems to us difficult, if not impossible, to distinguish between these normal variations and any possible effect of roentgen therapy.

As would be expected from the experience gained in treating other tumours by irradiation, the more rapidly growing types mentioned above are by far the most sensitive. However, there would seem to be good reason for treating in a similar manner other more slowly growing tumours composed of more mature cell types, because some of these have a tendency to undergo malignant transformation and in this condition they would theoretically be sensitive to irradiation. It is therefore believed that in these cases irradiation should be given following partial and even supposedly complete surgical extirpation. Thus, while at the present time roentgen radiation may be regarded as the main therapeutic agent in the case of medulloblastoma and glioblastoma multiforme, it is at the same time to be regarded as being an important accessory to surgery in the treatment of some other more slow-developing gliomata, notably the protoplasmic astrocytomata and the oligodendrogliomata.

There are some (Cutler, Sosman and Vaughan [8]), who consider that in certain cases roentgen treatment should replace surgery, especially in the medulloblastomata, since lasting result cannot be accomplished by the latter. We believe, however, that in every case an exploration should precede irradiation, and this for two reasons. In the first place, it is not possible to make with certainty an accurate diagnosis of the tumour type. By irradiating a lesion such as a cystic astrocytoma of the cerebellum, which is very amenable to surgical treatment, valuable time will be lost and irreparable damage may develop, even if the lesion be later successfully treated surgically. Some believe that irradiation might be regarded as a therapeutic test for medulloblastoma, but cases have been described in which temporary improvement has followed similar treatment of cerebellar astrocytomata, and very serious diagnostic errors are likely to be made if such a belief becomes general. Such temporary improvement is indeed to be expected if irradiation diminishes the secretion of cerebrospinal fluid [22]. In the second place it is considered that surgery should always precede irradiation, since it allows of a decompression being made and thus reduces the dangers of the reaction which so frequently follows irradiation and which is presumably due to swelling of the tumour and its surroundings with a resulting rapid rise in intracranial pressure.

The question of technique and dosage of radiation will now be discussed. Irradiation therapy rests upon an empirical basis because practically nothing is known of the mechanism of action of X-rays and gamma rays upon living protoplasm, or why malignant neoplastic cells are frequently more profoundly influenced than normal cells. Clinical experience furnishes the only guide at present for the mode of administration of irradiation in the treatment of neoplasms. In the case of cutaneous carcinomas large doses varying from 5,000 to 6,000 r. will destroy practically all basal-celled carcinomata of small or moderate size, and will also sterilize the majority of small squamous-celled growths. In squamous-celled carcinomas of the nasopharynx, tonsils and larynx, a tumour-dose of approximately 4,500 r. appears to afford the optimum opportunity for destruction, and clinical experience would indicate that approximately 20 to 25 per cent. of such cases may be controlled locally for five years or more.

There is little more than these positive observations to afford a basis upon which to develop a technique for the irradiation of intracranial neoplasms, and indeed experience with radio-resistant epithelial tumours (colon, stomach, &c.) would indicate that these observations might not at all be applicable to brain tumours.

Tissue Tolerance.

The optimum method for irradiation of neoplasms would seem to be the administration of the optimum dose with minimum reaction in the surrounding normal tissues. Clinical experience has shown that where excessive doses have been administered, resulting in serious damage to the normal tissue, the neoplasm is not controlled. The optimum dose for the destruction of the neoplasm would appear to be a dose that is less than the minimal one for permanent damage to the normal tissues. The margin between these two doses may well be a very narrow one. Thus the maximum normal tissue-tolerance-dose would represent a point beyond which irradiation is futile and harmful. From the cases cited above, it would appear that large doses of the magnitude of 15,000 r., even though administered during a series of treatments extending over several months, are excessive, and eventually induce irreparable damage in the brain without destroying or permanently controlling the growth of the glioma.

Optimum Dose.

Whether the optimum tumour-dose of 4,500 r. which appears to obtain for nasopharyngeal squamous-celled carcinomata also holds for intracranial tumours is a question that can be ascertained only by further clinical observations. The best result obtained in the small series reported above was in the case treated in a manner somewhat similar to that employed in naso-pharyngeal carcinomas. This dose may be delivered to cerebral tumours which are not too deeply situated, by making use of a single portal situated directly over the tumour. This portal should not exceed an area of 100 sq. cm. and daily doses of 150 r. may be given for forty days. Two opposing portals, but of smaller size (8 by 8 or 6 by 6), may also be employed, administering 3,000 r. to each over a similar total period. In deeply situated neoplasms three or more portals may be necessary to obtain a tumour-dose approximating 4,000 to 4,500 r.

In the case of the medullablastoma, which is highly sensitive to irradiation in that there is immediate and rapid regression, the problem of irradiation therapy may be quite similar to that in lymphoblastoma, where there is immediate response, but an ultimate high degree of radio-resistance. Limited experience would indicate that the optimum tumour-dose, not for cure, which may be impossible, but for prolonged control of the neoplasm, is somewhat less than 4,500 r. In Hodgkin's nodes for example, the tissue effects produced by 700 r. in one case and 3,000 r. in another case, were found to be identical.

It is, of course, frequently impossible to administer such large doses. Irradiation therapy once begun must be discontinued in many instances after relatively few treatments because of the general depression and the poor condition of the patient. However, in planning courses of therapy, the tumour-dose of 4,000 to 4,500 r. may be envisaged as a goal to be obtained if at all possible.

Time Factor.

The time-factor is of prime importance in the irradiation therapy of tumours, because wide variations in tissue reactions are produced when a given large dose is administered in one sitting, divided between several succeeding sittings or fractionated in short series, alternating with periods of rest. The principal reason for this is the factor of cell-recovery from the effects of irradiation. Obviously a quantity of irradiation, if delivered in a short period, may produce normal tissue-damage resulting in a failure of the treatment, while the same dose administered in proper chronology may affect the destruction of the neoplasm. There is still a question as to the proper time-factor for the treatment of naso-pharyngeal carcinomas, where numerous observations have been made. In the case of intracranial neoplasms, observations have been too few to permit of definite conceptions of what may be the proper time-factors. The question is further complicated in the case of brain neoplasms by the fact that the magnitude of normal tissue-reactions in the brain might produce general symptoms warranting cessation of treatment; whereas similar reactions in less vital regions are relatively well tolerated. Limited experience, however, would indicate that five or six weeks is a safe period in which to administer approximately 5,000 to 6,000 r. surface dose to one cranial portal of the size indicated.

Another point upon which there is still debate, is the importance of the intensity with which the irradiation is administered. It has been repeatedly shown that higher intensities produce more profound vascular reactions in the skin [22]. If this holds for the deeper structures as well, irradiation should be administered to the brain in intensities not exceeding 10 r. per minute, in order to avoid as much as possible unduly severe vascular reactions. For this same reason we feel that the administration of large doses in one sitting during the operation, while the bone flap is reflected (as recently recommended in some clinics [11]) is contrary to good judgment, and will not accomplish the desired results.

Limitations of the Irradiation Therapy of Gliomata.

It is generally agreed that irradiation is most effective in neoplasms of anaplastic cell-type and least effective where the cells are quite mature. In the present state of knowledge and experience in the irradiation therapy of the gliomata it would seem predictable from the cell-type, that a large percentage would fall into the category of those neoplasms which cannot be destroyed by present forms of irradiation. Restraint of growth may however be possible in an increasing number of cases as further experience is gained with various techniques.

CONCLUSIONS.

(1) Roentgen irradiation is capable of giving rise to degenerative changes in the tissues of the central nervous system. These changes involve not only the nerve-cells, but also the neuroglia and blood-vessels.

(2) The alterations in vascular structure do not appear to be responsible for the production of the parenchymal changes. Both are the result of irradiation.

(3) Roentgen therapy, preceded by accurate pathological diagnosis and a decompression, is of value in the treatment of the gliomata. Medulloblastoma, and to a less extent, glioblastoma multiforme, react most favourably to this treatment.

(4) Since certain of the more benign gliomata possibly undergo malignant dedifferentiation, surgical treatment of these should be followed by roentgen irradiation in an effort to prevent or retard this change.

(5) In view of the damage to the normal brain which may be produced by large surface doses of irradiation, suggestions are put forward as to what may be a more suitable method of employing roentgen therapy.

One of us (J. E. A. O'C) carried out his part of this work when attached to the service of Dr. Percival Bailey, as a Rockefeller Foundation Fellow, and must express his indebtedness to Dr. Bailey for the opportunity to pursue the investigation, for his advice in connection with the preparation of the histological specimens, and especially for his invaluable assistance in evaluating the changes observed.

REFERENCES.

[1] Alpers, B. J., and Pancoast, H. K. "The Effect of Irradiation on Normal and Neoplastic Brain Tissue," *Amer. Journ. Cancer*, 1933, **17**, 7.

[2] Bailey, P., "Further Notes on the Cerebellar Medulloblastomas; the Effect of Roentgen Radiation," *Amer. Journ. Path.*, 1930, **6**, 125.

[3] Bailey, P., Sosman, M. C., and van Dessel, A. "Roentgen Therapy of Gliomas of the Brain," *Amer. Journ. Roentgenology and Radium Therapy*, 1928, **19**, 203.

[4] Biondi, G. "Über eine in der Umgebung von Hirngeschwulsten vorkommende Veränderung," *Zeitschr. f. d. ges. Neurol. u. Psych.*, 1933, **149**, 129.

[5] Brunner, H., and Schwartz, G. "Einfluss der Rontgenstrahlen auf das reifende Gehirn," *Wiener klin. Wochenschr.*, 1918, **31**, 587.

[6] Brunschwig, A., and Perry, S. P. "High versus Low Intensity Irradiation in the Treatment of Carcinoma," *Radiology*, 1936, **26**, 706.

[7] Caspar, J. "Über die Veränderung des Hirngewebes insbesondere der Neuroglia in der Umgebung der Hirngeschwülste," *Zeitschr. f. d. ges. Neurol. u. Psych.*, 1933, **145**, 209.

[8] Cutler, E. C., Sosman, M. C., and Vaughan, W. W. "The Place of Irradiation in the Treatment of the Cerebellar Medulloblastoma," *Amer. Journ. of Roentgenology and Radium Therapy*, 1936, **36**, 429.

[9] Derry, E. M. "Remarks on the Effect of Rœntgen Therapy upon Gliomas," *Bull. Neurol. Inst. of New York*, 1936, **4**, 472.

[10] Demel, R. "Tierversuche mit der Rontgenbestrahlung des Cerebrum," *Strahlentherapie*, 1926, **22**, 333.

[11] Elsberg, C. G., Davidoff, L. M., and Dyke, C. G. "Rœntgen Treatment of Tumours of the Brain, &c.," *Surg. Gyn. and Obst.*, 1936, **63**, 794.

[12] Fischer, A. W., and Holfelder. "Lokales Amyloid im Gehirn. Eine Spatfolge von Rontgenbestrahlungen," *Deutsch. Zeitschr. f. Chir.*, 1930, **227**, 475.

[13] Globus, J. H. "Die Umwandlung gutartiger Gliome in bösartige spongioblastome. Ein *Beitrag zur Frage der gliogen* Geschwulste des Nervensystems," *Zeitschr. f. d. ges Neur. u. Psych.*, 1931, **134**, 325.

[14] Lorey, A., and Schaltenbrand, G. "Pachymeningitis nach Rontgenbestrahlung." *Strahlentherapie*, 1932, **44**, 747.

[15] Löw-Beer, A. "Zur Frage der Strahlenbehandlung intrakranieller Tumoren," *Ibid.*, 1935, **52**, 617.

[16] Lyman, R. S., Kupalov, P. S., and Scholz, W. "The Effect of Rœntgen Rays on the Central Nervous System," *Arch. Neurol. and Psych*, 1933, **29**, 36

[17] Markiewicz, T. "Über Spatschadigungen des menschlichen Gehirns, durch Rontgenstrahlen," *Zeitschr. f. d. ges. Neurol. u. Psych.*, 1935, **152**, 548.

[18] Müller, W. "Anderung des Gewebscharakters nicht radikal operierter Gliome," *Zeitschr. f. d. ges. Neurol. u. Psych.*, 1933, **148**, 469.

[19] Sachs, E., Ruberstein, J. E., and Arnisen, A. R. "Results of Roentgen Treatment of a Series of 110 Gliomas," *Arch. Neurol. and Psych.*, 1936, **35**, 597.

[20] Scholz, W. "Über die Empfindlichkeit des Gehirns fur Röntgen und Radiumstrahlen," *Klin. Wochenschr.*, 1935, **14**, 189. See also *Deutsch. Zeitschr. f. Nervenheilk.*, 1935, **136**, 133.

[21] *Idem.* "Experimentelle Untersuchungen uber die Einwirkung von Rontgenstrahlen auf das reife Gehirn," *Zeitschr. f. d. ges. Neurol. u. Psych.*, 1934, **150**, 765.

[22] Skefer, D. G. "Roentgen Rays and the Central Nervous System," Press of the Azov., Black Sea Region, Rostov. on Don, 1936, 243 pp.

[23] Stern, F. "Die psychischen Störungen bei Hirntumoren und ihre Beziehungen zu den durch Tumorwirkung bedingten diffusen Hirnveränderung," *Arch. f. Psych.*, 1914, **54**, 563.

[24] Schaltenbrand, G. "Epilepsie nach Rontgenbestrahlung des Kopfes im Kindesalter," *Nervenarzt*, 1935, **8**, 62.

EXPLANATION OF PLATES.

PLATE IX.

FIG. 1.—Degenerating vacuolated pyramidal cell in the left central region. Bielschowsky, × 600. Case 3.

FIG. 2.—Fatty degeneration of adventitial cells of a small cortical blood-vessel in left prefrontal region. Herxheimer, × 300. Case 3.

FIG. 3.—Two microglial cells filled with lipochrome granules. From the left temporal subcortex. Herxheimer's method, × 600. Case 5.

FIG. 4.—Hypertrophied microglial cell from the cortex of the right frontal region (rod-cell). Hortegas silver carbonate, × 600. Case 4.

FIG. 5.—Macrophages gathered around small cortical blood-vessel in the right parieto-occipital region. Nissl, × 300. Case 4.

FIG. 6.—Swollen protoplasmic astrocytes, some undergoing clasmatodendrosis, from the cortex of the right parietal region. Cajal's gold sublimate, × 600. Case 4.

FIG. 7.—Swollen protoplasmic astrocyte from region of the left basal ganglia. Cajal's gold sublimate, × 600. Case 4.

PLATE X.

FIG. 1.—Small patch of ischæmic necrosis from the cortex of the left paracentral lobule. Nissl, × 110. Case 4.

FIG 2.—Small softening in the cortex of the right middle temporal gyrus. Nissl, × 110. Case 4.

FIG. 3.—Swollen hypertrophied neuroglial cells from the cortex of the left middle temporal gyrus. Nissl, × 430. Case 4.

FIG. 4.—Unusual glia wall formation about blood-vessels in the right frontal cortex. Nissl, × 215. Case 4.

PLATE XI.

FIG. 1.—Case 5.—Tumour removed at operation before roentgen irradiation. Structure that of a typical medulloblastoma. Hematoxylin-oesin, × 150.

FIG. 2.—Case 5. Tumour from cerebellum obtained at necropsy after intensive irradiation. For comparison with previous photograph. Hematoxylin-oesin, × 150.

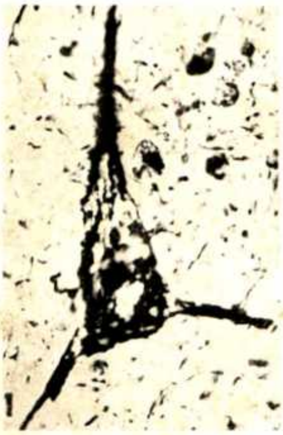
FIG. 3.—Main mass of tumour; case W. M. Structure that of a typical protoplasmic astrocytoma. Hematoxylin-eosin, × 300.

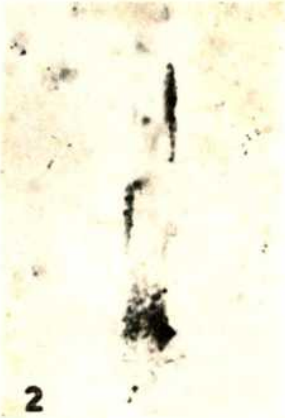
FIG. 4.—Nodule in centre of tumour; case W. M. Focus of increased malignancy. Hematoxylin-eosin, × 300.

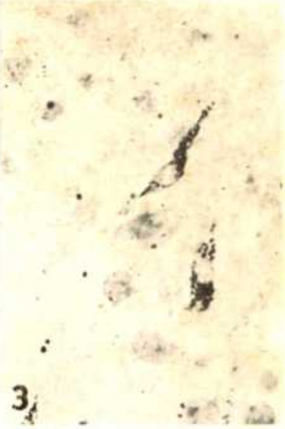
FIG. 5.—Tumour from Case 3 at necropsy. Protoplasmic astrocytoma. Hematoxylin-eosin, × 300.

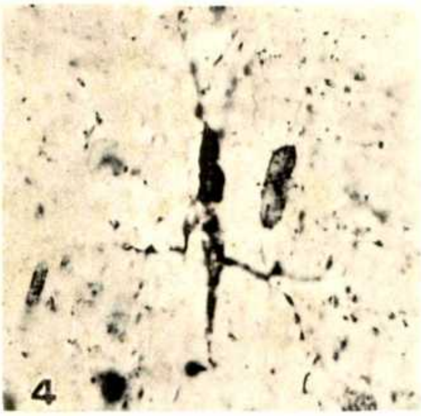
FIG. 6.—Tumour from Case 4 at necropsy. Protoplasmic astrocytoma. Hematoxylin-eosin, × 300.

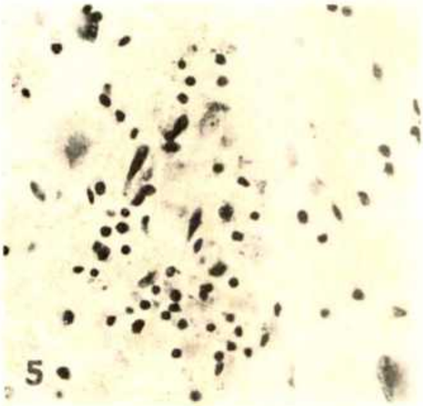
PLATE IX.

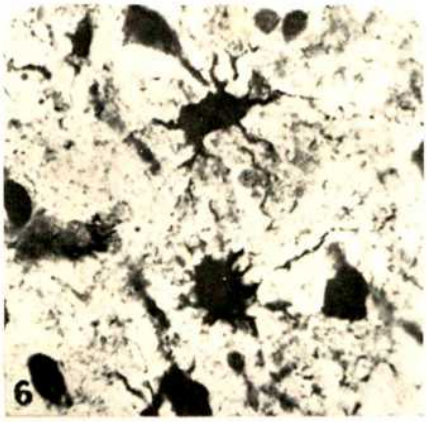


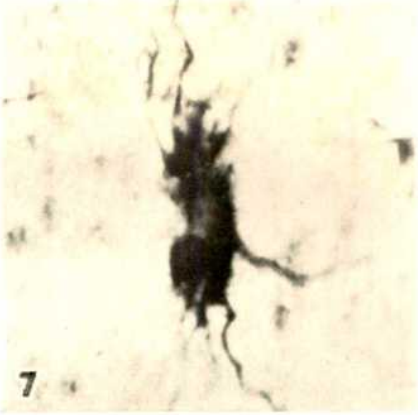






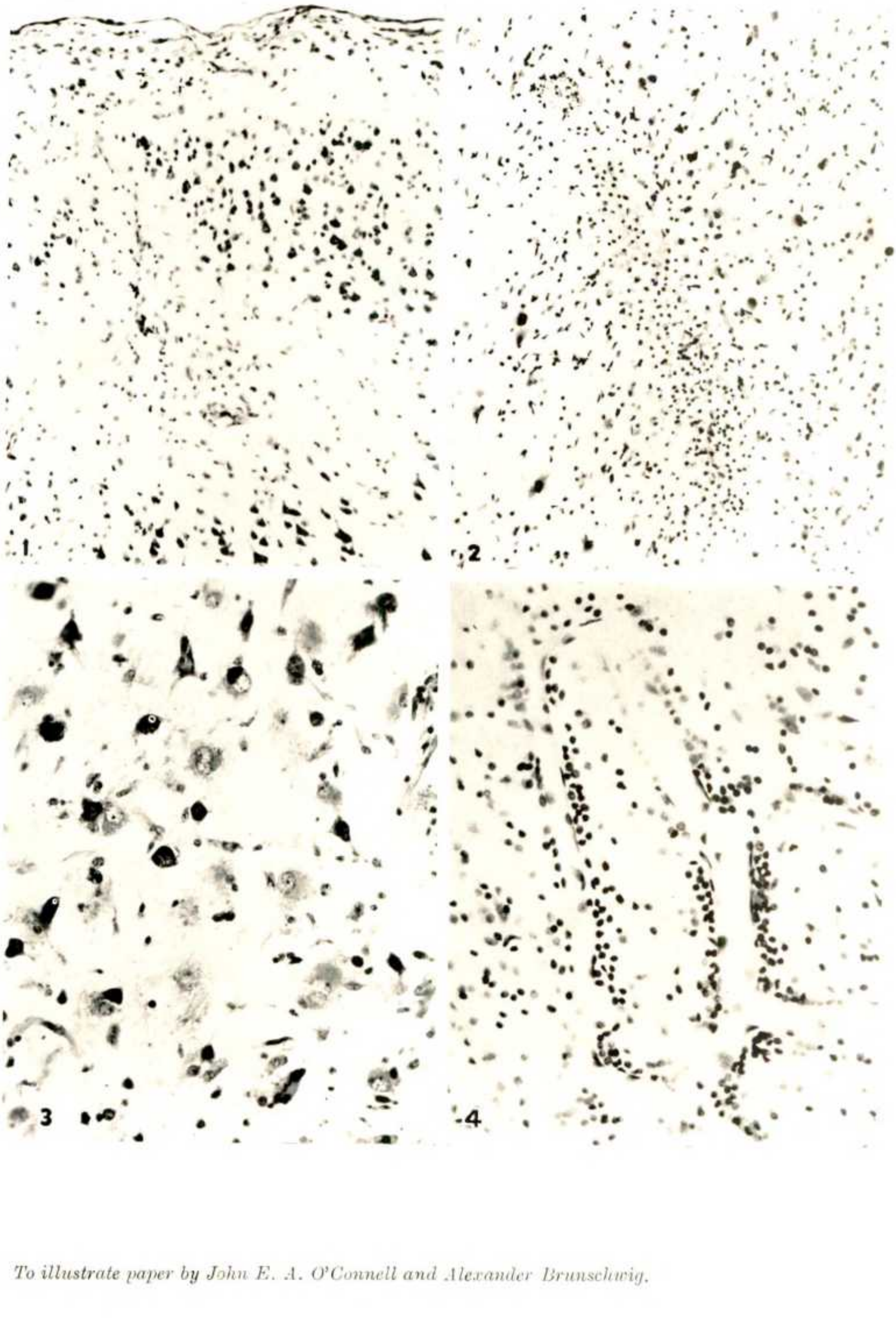






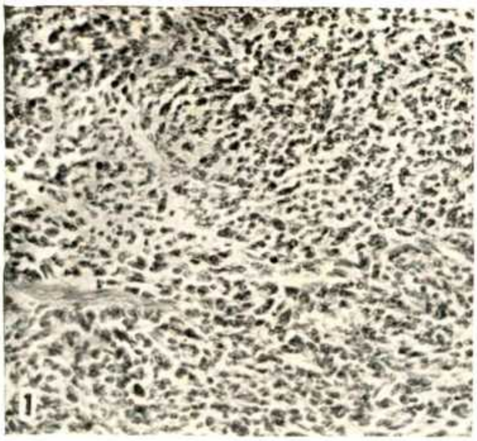
To illustrate paper by John E. A. O'Connell and Alexander Brunschwig.

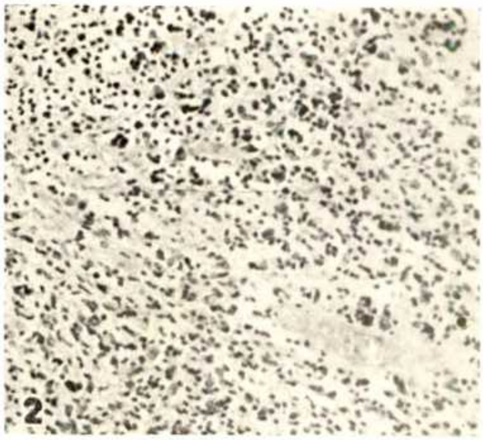
PLATE X.

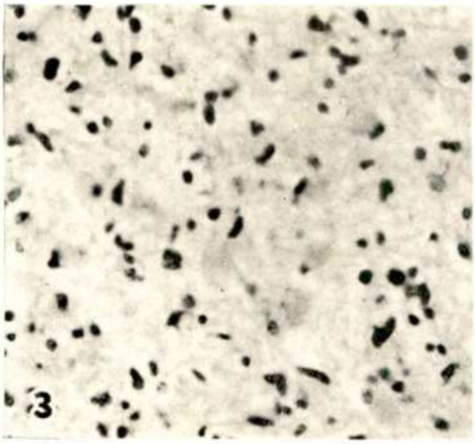


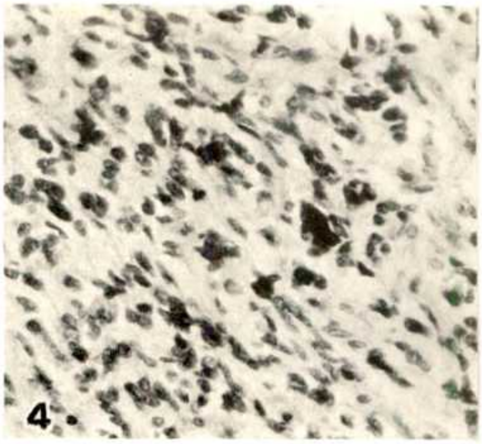
To illustrate paper by John E. A. O'Connell and Alexander Brunschwig.

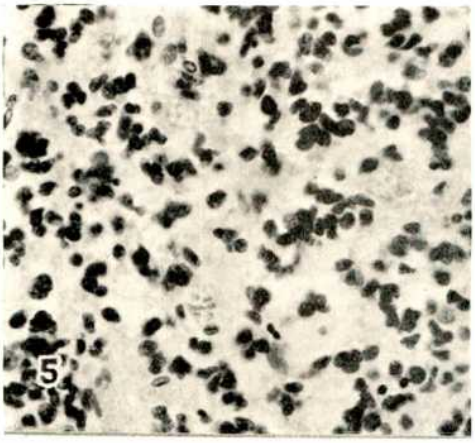
PLATE XI.

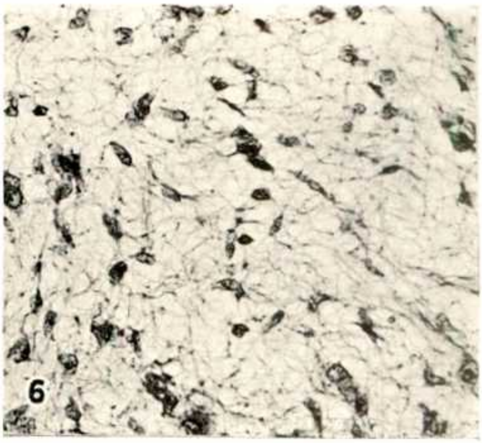












To illustrate paper by John E. A. O'Connell and Alexander Brunschwig.

A CLINICAL STUDY OF THE RESPIRATORY MOVEMENTS IN HEMIPLEGIA.

BY LAWRENCE C. KOLB AND FRANÇOIS KLEYNTJENS.[1]

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INTRODUCTION.

THAT the respiratory movements of the chest are modified on the hemiplegic side of the body has long been known, but the nature of these changes has been variously stated. Broadbent [2] noting, among other things, that respiratory movements still occurred on the hemiplegic side stated his theory of bilateral cortical representation of certain movements. Hughlings Jackson [10] declared that in cases of both early and late hemiplegia the respiratory movement of the thoracic cage is greater in quiet breathing on the affected side than on the normal side, but is of slightly less amplitude than it is on the normal side during deep voluntary inspiration. He further postulated that motor fibres pass directly from the cortex to the phrenic and costal centres of the cord controlling the respiratory muscles, while an inhibitory pathway exists between the cortex and the "superior respiratory centre" in the medulla.

Numerous writers [1, 11, 12, 13, 14, 15] state that the respiratory movements are decreased on the hemiplegic side. Grawitz [7] recorded kymographically the movements of both sides of the chest in thirty cases of hemiplegia, and found the excursion during quiet breathing was diminished in twenty-two. One case showed an increased expansion on the affected side which he ascribed to "crossed paralysis." Dejerine [5], after perimetric studies of the chest in inspiration and expiration, decided that the excursion is only diminished on the affected side in forced respiratory movements involving the accessory respiratory muscles. In ordinary breathing the amplitude is equal on both sides except in patients who being hemiplegic since childhood and having maldeveloped musculature show a decrease on the affected side.

Strümpell [19] stated that the diminished expansion on the affected side explains the observation that pulmonary disease is more often localized at the base on the affected side, and Faschingbauer [6] described clinical signs of basal atelectasis here.

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[1] Fellow of the C.R.B. Educational Foundation.

Starr [18] declared that during coma and the period of shock inspection of the chest usually shows that the respiratory movements are more active on the paralysed side. On the other hand, Ross [16] described depression of respiration on the affected side in the first few days after the cerebral injury. The clinical study of a few cases suggested that the conflicting opinions might be clarified by a more careful graphic examination.

METHODS.

An apparatus was constructed for simultaneously recording the movements of both sides of the chest. This consists of two small rubber balloons; each is connected by rubber tubing to a similar balloon stoppered into a bell jar. The bell jars in turn communicate with Marey tambours, the movements of which record on a kymograph. The free balloons are applied under a cardboard shell which is fastened to the chest by equal lengths of 2 in. adhesive tape extending from the posterior axillary line to just lateral to the costo-chondral junctions. A quantity of air is injected into these balloon systems which are connected by a cross piece of rubber tubing. This is then closed with a stop cock. The movements of the kymograph points are then checked by injecting 2 and 4 c.c. amounts of air into each system and measuring the deflections of the writing points on the kymograph. The time recorder was used in a few cases, but no additional information was obtained.

Kymographic tracings were obtained from three normal individuals, one case of pneumothorax, two cases of acute hemiplegia, fifteen cases of old hemiplegia, and one unilateral Parkinsonian syndrome. The cases of chronic hemiplegia are divisible into two groups: the first includes eight cases of spastic hemiplegia, while the second includes six cases of flaccid hemiplegia. The latter group consists of one case with a motor paralysis alone, and four with combined sensory-motor defects. A case of hemianesthesia without any motor defect is also included. This group is an unusual one and is intended to give no true significance as to the incidence of such cases. We were fortunate in being able to choose suitable patients from a series of over a hundred cases of hemiplegia in the chronic wards of the Baltimore City Hospital. Besides recording quiet respiratory movements and deep voluntary inspirations, we also studied the effects of hyperpnœa induced by inhaling carbon dioxide in seven cases. Five other individuals were examined clinically, of these two were in deep coma and three had spastic hemiplegia.

RESULTS.

As the findings in each group were constant, only the records from typical cases are presented here.

Case 1.—The first record (fig. 1) is that obtained from a healthy young individual. The tracing from the right side of the chest is placed below that on the left. The smaller waves are those during quiet respiration ; the larger waves represent a single deep inspiration performed on command. To the right is a record from the same individual in hypernea following inhalation of carbon dioxide. Careful measurements with calipers show no variation in the size of the simultaneous movements of the two sides of the chest wall.

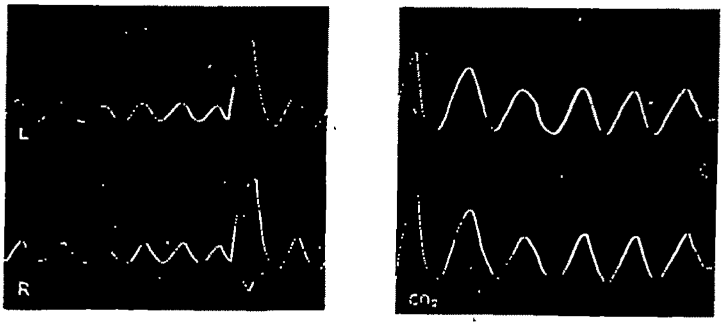

FIG. 1.—*Case* 1. Kymographic record of respiration of a normal individual. The upper record is that from the left side of the thorax, the lower from the right. On the left half of the record, the smaller waves are those of quiet respiration and the single large wave one of maximal inspiration. The tracings on the right were taken during hyperpnœa.

Case 2.—W. T. (J.H.H., U. 741716). The following case is an example of acute hemiplegia seven days after the cerebral lesion. This 33-year old negro was admitted to the hospital, complaining of shortness of breath and swelling of his ankles. He was treated as a case of rheumatic heart disease with aortic insufficiency and cardiac decompensation. Seven days after admission he suddenly became disorientated, and later became stuporous. The next day he had a flaccid paralysis of the left face, arm and leg. The respiratory tracing was taken six days later. The left side of the face was flattened, and he was unable to innervate the facial muscles, although the frontalis contracted bilaterally. The tongue deviated to the left. Both the left arm and leg lay flaccidly in extension and were hypotonic on passive movement. Sensation could not be tested, as he was still confused. The tendon reflexes in the arms were equal but sluggish. The left abdominal and cremasteric reflexes were absent, and the left knee and ankle-jerk were less brisk than those on the right. No clonus was obtained. Hoffmann and Babinski signs were noted on the left.

The kymographic record (fig. 2) shows that the movements of the left side of the chest are diminished as compared with the normal right side. He was unable to execute voluntary expansion as he failed to understand commands; the arrows on the record indicate where such requests were made. However, in the tracings and observations made from the other cases of early hemiplegia voluntary movements were likewise diminished on the affected side.

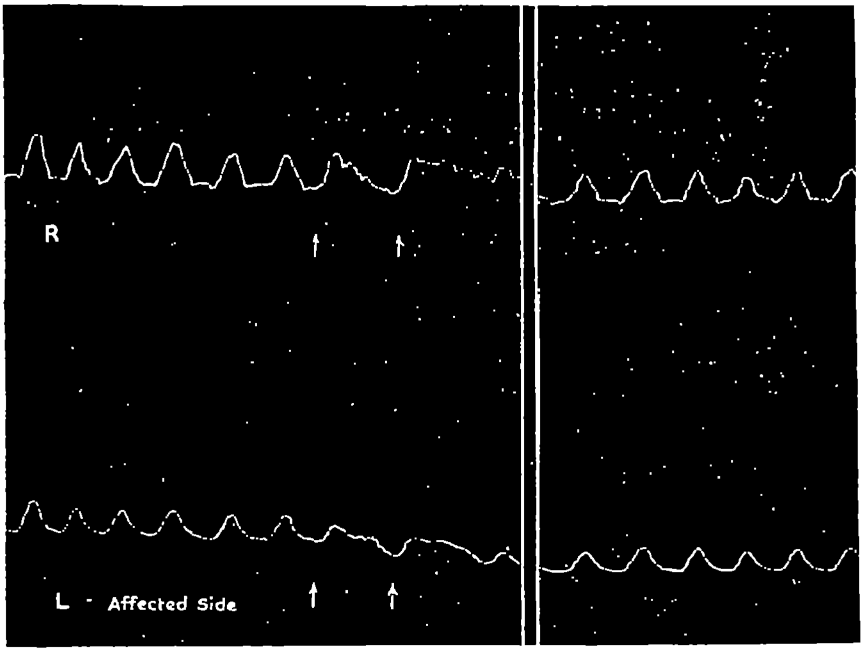

FIG. 2.—*Case* 2. Acute left hemiplegia seven days after cerebral accident. Right thorax recording above, left thorax below. Arrows indicate suggestions of voluntary inspiration not attempted by the patient.

Case 3.—H. R. (B.C.H., U. 19254). This case summarizes the findings in the group of spastic hemiplegics. A 40-year old negro ship's cook was admitted to the hospital complaining of left-sided paralysis of twenty years' duration. He had been struck on the head by a swinging door when his ship sank during the War, and on being carried off the vessel his left side was found to be paralysed. Since then his leg and arm have remained stiff and weak. The general physical examination was normal. On neurological examination the cranial nerves were normal, with the exception of a lower facial weakness and deviation of the tongue to the left. There was a marked spastic paralysis of the left arm and leg. The arm was carried adducted at the shoulder, flexed to 70° at the elbow and flexed and pronated at the wrist. The muscles about the shoulder girdle were strongly contracted. This was particularly noted in the pectoralis major. The left rectus abdominis was more tense than the right. The left leg was maintained in 45° flexion at the hip and the same degree of flexion at the knee. Sensation was undisturbed. The tendon reflexes were all over-active on the left. The abdominal and cremasteric reflexes were not obtained and the Hoffmann and Babinski signs were present on the left. No clonus was noted.

On inspection of his chest, it was seen that both in normal and deep voluntary breathing the movements of the paretic side were decreased. This is borne out by the kymographic record (fig. 3). The second half of the record is that obtained following inhalation of carbon dioxide. At V_2 and V_3 are shown two voluntary inspirations. Between V_2 and V_3 we see the movements of the chest in hypernoea, and it is apparent that the amplitude is increased to a greater extent on the paralysed side than on the normal side. At H the inspiratory wave on the normal side measures only 1 cm. in the original, which is comparable to the waves during quiet respiration shown in the first part of the record. However, on the paretic side the amplitude is likewise 1 cm., an expansion never reached during quiet breathing. This increase in amplitude on the affected side is not true for attempted voluntary inspiration during the period of hyperpnœa. This was also observed in two other cases during study of hyperpnœa.

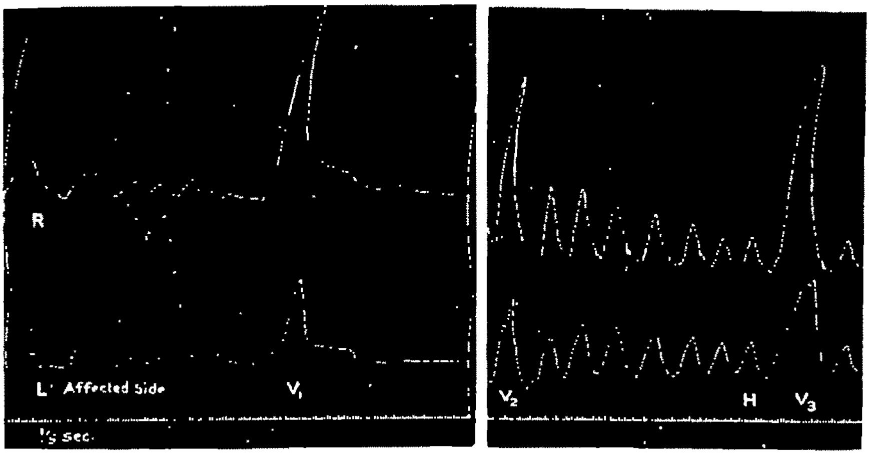

FIG. 3.—*Case* 3. Spastic left hemiplegia of twenty years' duration. Right chest recording above, left below. V_1, V_2, V_3, are voluntary inspirations. Right half of tracing records activity in hyperpnœa.

Case 4.—M. J. (B.C.H., 7999) presents a flaccid hemiplegia with no sensory changes whatsoever. He is the only case of this type examined. He is a 45-year old coloured male stevedore who came to the hospital complaining of shortness of breath and palpitation. He was treated as a case of rheumatic heart disease with mitral insufficiency and decompensation. Seventeen days after his second admission in 1936 he woke in the morning and realized that his right face, arm and leg, were limp and useless. His condition gradually improved so that he was able to get around in a wheel chair.

A neurological examination was done four months after the onset of his paralysis at the same time the kymographic records were made. The cranial nerves were normal except for slight weakness of the masseter and pterygoid muscles on the right. The right side of the face was flattened and all movements of the muscles lost except wrinkling of the brow. The palate moved less rapidly on the right than the left and the tongue deviated to the right. The right trapezius and sternomastoid were weaker than those on the left.

There was complete loss of voluntary movement in the right arm and leg beyond the ability to raise the shoulder slightly and weakly flex and abduct the thigh on the abdomen. The right arm lay flaccidly at his side. The right side of the chest moved with greater amplitude than the left in both quiet breathing and voluntary inspiration. The abdominal muscles were weaker on the right, and the leg on the same side was also hypotonic. There was atrophy of both the arm and thigh on the paretic side. No sensory changes were found. The tendon reflexes were equal but sluggish on both sides. A right Hoffmann but no Babinski response was obtained. The abdominal reflexes fatigued less easily on the left. He was diagnosed as a chronic flaccid motor hemiplegia.

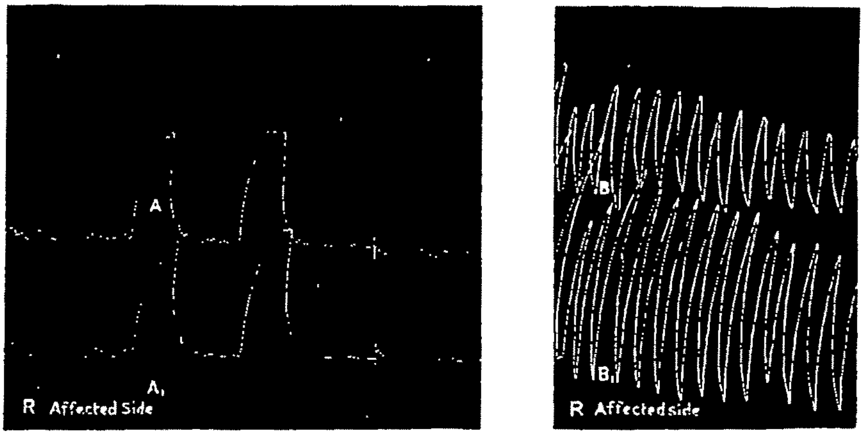

FIG. 4.—*Case* 4. Flaccid right hemiplegia of four months' duration. Left chest recording above and right below. Recording during hyperpnœa on the right half of the graph.

On the left of the kymographic tracing (fig. 4) are presented the respiratory waves during quiet breathing and two waves of maximal voluntary inspiration. It is apparent that both are greater on the affected side. The cardiac apical impulse distorts the respiratory waves recorded from the left chest.

On the right side of the chart is presented the tracing obtained during hyperpnœa. The greater amplitude on the affected side is striking. Again we notice that during hyperpnœa the amplitude of movement on the paretic side is increased out of proportion to that on the normal. This is made clearer if we compare the maximal voluntary inspiration on the normal side during quiet breathing with a wave of the same size during hyperpnœa, for instance A and B. Now if we compare the simultaneous waves on the affected side A_1 and B_1 we find that during hyperpnœa the wave on the paretic side is double that during voluntary breathing.

Case 5.—F. N. (B.C.H., U. 12693) has a hemianæsthesia with hypotonia, but no loss of motor power although movements are not performed with the usual facility on the affected side. He is a 60-year old white male labourer who was admitted to the hospital complaining of paralysis of the left arm and leg. Five years previously he suddenly suffered a tingling paræsthesia of the left arm and leg followed by weakness of the extremities, slight difficulty in speaking and urinary incontinence. He remained in bed, but on getting up seven weeks later had a similar seizure. Since then he has been unable to walk as he cannot support his weight on the left leg. He is, however, able to move both the arm and leg with considerable force. He has had several clonic convulsive seizures involving the left arm and leg since his admission. His general physical examination was normal except for considerable emphysema. The blood Wasserman and flocculation tests were reported as +4 ; the cerebrospinal fluid was clear and its Wasserman reaction negative.

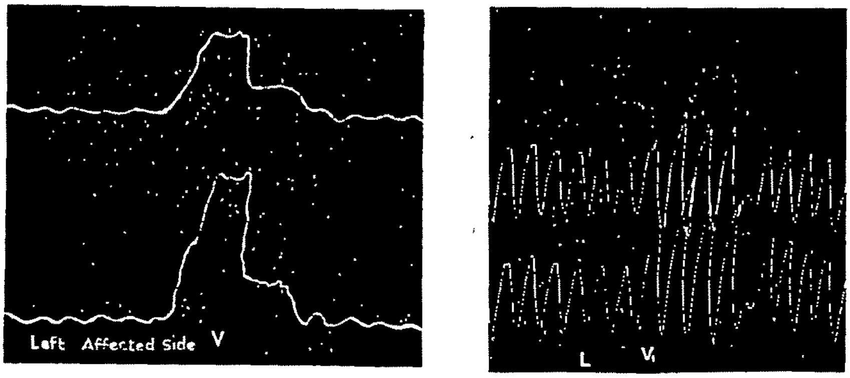

FIG. 5.—*Case* 5. Left hemianæsthesia of five years' duration. Right chest recording above, and left below. V_1 and V_2 indicate voluntary inspirations. Recording during hyperpnœa on the right.

The neurological examination, eight years after the onset of his illness, showed a fairly co-operative man, fatiguing easily, but in no distress. He was able to get about in a wheel chair. Over the left side of the head and face thermal, tactile, and painful sensations were greatly impaired and two-point sensation was lost. There was no loss of power in the muscles of mastication. The left facial muscles were hypotonic with flattening of the nasolabial fold. Movements of these muscles were strong. The gag reflex was sluggish. The tongue was protruded to the left, but immediately afterward this position was corrected. The margins of the tongue were furrowed.

Examination of the motor system showed no weakness of any limb, but the muscles of the left arm and leg were hypotonic as evidenced by the subluxation present at all the joints on this side. This was so marked that dislocation of the shoulder could be easily produced either actively or passively. The muscles felt relaxed and showed a measurable atrophy.

Sense of passive movement and position, discrimination of Weber's compass points and deep pain sensation were lost over the whole left side. Tactile stimuli were appreciated over the face alone but only the extremes of hot and cold were felt elsewhere. These were often misstated. Painful stimuli were delayed and not very acute when felt.

The tendon reflexes were all equal and sluggish. There was no clonus, nor were Hoffmann or Babinski signs obtained. The abdominal reflexes were present in both superior quadrants but not in the inferior. There were no cremasteric reflexes.

The respiratory record (fig. 5) shows, as in the previous case, a larger amplitude of expansion on the affected side in both quiet and voluntary breathing. The increase on voluntary breathing is marked. In hyperpnœa, the amplitude of movement is not greatly increased on the affected side, although there is an increase in the amplitude of voluntary respiratory movements performed during this same period as shown at V_1.

Case 6.—M. D. (B.C.H., 12756) is representative for the group of four sensori-motor hemiplegics with flaccid palsies. This 52-year old coloured labourer came into the hospital in 1933, saying he had had a stroke. He was acutely ill. Temperature 103, pulse 90, respiration 20, blood-pressure 160/90. The chest expansion at this time was recorded as being limited on the left side. Percussion was normal, but auscultation revealed râles at the right base and axilla clearing after cough. There were signs of aortic insufficiency, but the rest of the general examination proved negative. On neurological examination there was paralysis of the face, arm and leg associated with a spasticity in the limbs, but the arm was carried in extension rather than in the usual flexed hemiplegic position. There was pitting œdema of both the left hand and leg. Sensation of tactile, thermal and painful stimuli were impaired over the whole extent of the left side of the body. Vibratory sensation, sense of passive motion and position and two point sensation were lost. Astereognosis was present on the left. The left biceps, triceps, supinator, knee and ankle-jerks were over-active, while the abdominal and cremasteric reflexes were diminished. There were a sustained wrist and an unsustained ankle clonus, but no Babinski or Hoffmann signs.

The urine, blood, and cerebrospinal fluid studies were normal, but the blood Wasserman and Kahn tests were reported as +4.

He continued to have painful pricking sensations over his left side, and at least on one occasion he felt an unusual sense of well-being in the same area.

On March 2, 1934, he had another "stroke" which increased the defect of movement in his arm and hand. His original spastic palsy now changed and with increasing flaccidity he had to take to a wheel chair. In August of 1936 it was noticed that he was running a remittent fever. On physical examination signs of a pleural effusion were present over the left lung base. Twice in October thoracentesis was performed and 800 c.c. of straw-coloured fluid was obtained. Fluid was still present by X-ray in September, 1936.

The neurological examination was repeated in September. He now appeared thin and emaciated, he was irritable but otherwise a good observer. The cranial nerves were essentially as reported before. He had no voluntary movement of the left extremity. There was atonia of all the musculature on the left side of the body with measurable atrophy of the arm and forearm, thigh and leg. The left arm lay flaccidly extended by the side, there was a gap between the acromial tip and the head of the humerus. Subluxation was present at the left knee and ankle-joints and this limb lay flaccidly in a position of extension and external rotation. He pushed it about with his other foot. The sensory loss was extreme. Pain and the extremes of hot and cold, particularly the latter, gave rise to disagreeable sensations. Deep pain was delayed, but again often excessive. Vibratory impulses were dulled but when applied vigorously caused an intense boring feeling. The sense of passive movement showed the greatest disturbance in that even at the knee and elbows movement to 10° were not appreciated. The tendon reflexes remained increased on the left, with a sustained wrist clonus and an unsustained ankle clonus. There was no Babinski response or Hoffmann sign.

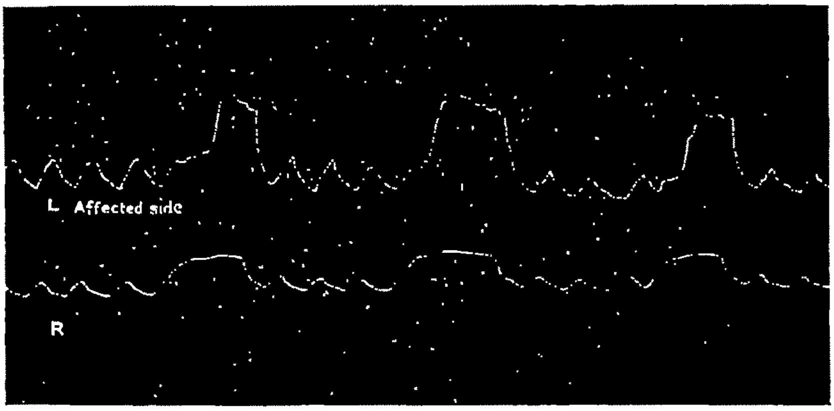

FIG. 6.—*Case* 6. Left flaccid sensori-motor hemiplegia. Left chest recording above and right below. Large waves are those of voluntary inspiration following command.

In December of 1936, with signs of pleural effusion still present in the left, the movements of his chest were recorded. It is evident that expansion is increased to a great degree, both in quiet and voluntary respiration at this time. There is thus an increase of movement on the flaccid hemiplegic side, although an underlying pleural effusion might be expected to reverse the picture. It is of interest, also, that while the hemiplegia was spastic a note was made that the movements of the paretic side of the chest were decreased, whereas with flaccidity we record an increase on the same side. The observations and records obtained from the other three cases in this group also showed an increase in amplitude in both quiet and voluntary movement as well as during hyperpnœa (fig. 6).

Case 7.—L. R. (B.C.H., 17605). The following case is one of pulmonary tuberculosis with an artificial pneumothorax and is added as a contrast to the former as well as demonstrating the use of the apparatus in other pulmonary disorders. This 20 year old white boy was admitted to the hospital on December 1, 1936, stating that he had recently coughed blood on several occasions. On examination the right shoulder was carried slightly lower than the left, and the right clavicle was more prominent, due to some atrophy of the muscles here. There was a diminished excursion at this apex with decreased breath sounds anteriorly below the left clavicle. Over the right apex posteriorly the breath sounds were harsh and after cough a few crackling râles were heard. A Roentgenograph of the chest showed increased hilar shadows with infiltration extending towards the base and apices. He was started on pneumothorax therapy and had a 600 c.c. refill an hour and one half before the respiratory kymographic record was made.

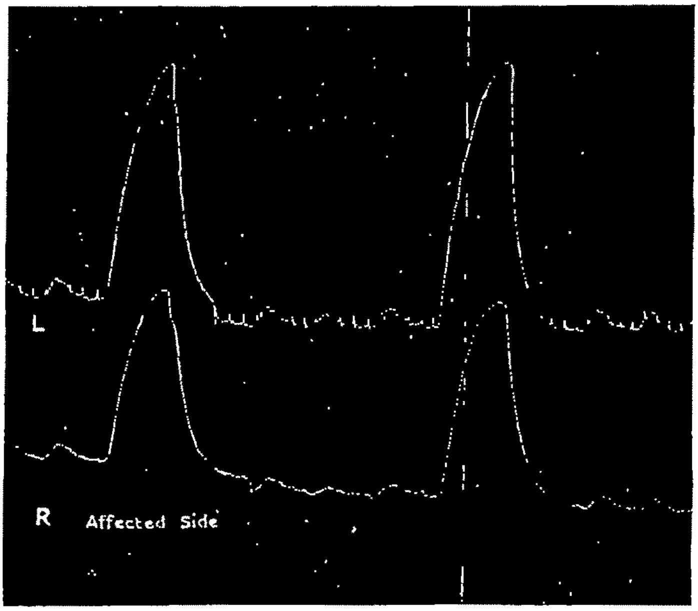

FIG. 7.—*Case* 7. Right pneumothorax therapy with refill one and a half hours previously. Left chest recording above and right below. Cardiac impulse shown distorting movements of left half of thorax.

The record (fig. 7) shows a decrease in quiet and voluntary respiration on the right side or the side of the pneumothorax. The record should be contrasted with that of the previous patient who showed an increased expansion on the paralysed side where he likewise had a pleural effusion.

Since the cases presented before suggest a relationship between spasticity and flaccidity and respiratory movements it seemed of interest to study a case of unilateral Parkinsonian syndrome. In this patient there was clear-cut rigidity on one side of the body although perhaps this rigidity cannot be directly compared with the spasticity seen in hemiplegia.

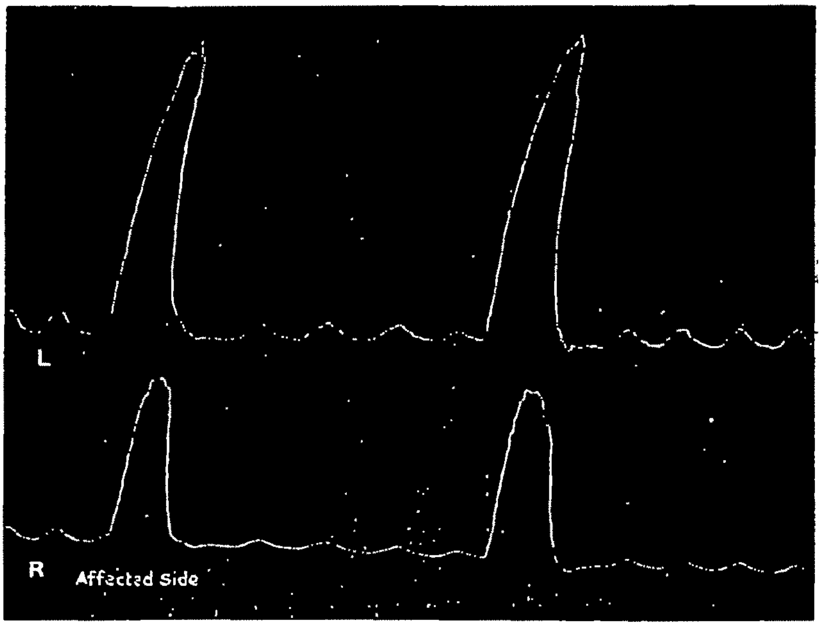

FIG. 8.—*Case* 8. Right hemi-Parkinsonian syndrome of nine months' duration. Left side recording above and right side recording below. Large waves are those of maximal voluntary inspiration.

Case 8.—(J.H.H., K. 99199). This 40 year old man showed the following neurologic abnormalities. His face was unusual in that the palpebral fissure was wider on the right and the facial muscles were immobile on that side. The right pupil was slightly larger than the left, but both reacted well to light and accommodation. The tongue was protruded to the right. There was a definitely increased rigidity to passive movements in the right arm and leg and a cog-wheel sensation was easily appreciated by passively flexing and extending the elbow. No tremor of the extremities was visible, but he had difficulty in fine movements of the right fingers. Sensation was undisturbed and the reflexes were within normal limits.

On inspection of his chest prior to recording the movements a slight lag was visible on the right side during maximal inspiration. The kymographic tracing (fig. 8) shows clearly the depression not only on voluntary inspiration but also during quiet respiration. The deflections of the writing point on the affected side are exactly one-half those on the normal throughout.

DISCUSSION.

Most observations on this subject have been made by inspection and palpation of the chest alone, and in many instances no changes in respiration were observed. A study of our cases fails to confirm certain of the conclusions of previous clinicians which we summarized in the introduction. Our charts present certain graphic evidence concerning reflex activity in the presence of flaccidity or spasticity.

The records and observations indicate that shortly after the cerebral accident causing hemiplegia and while the patient is still in the period of reflex depression, the amplitude of movement on the affected side of the chest is diminished in both quiet and voluntary respiration. Starr's [18] statement that the movements were increased during this period might possibly be explained, if his patients were cyanotic, on the basis of a specific excitation of the respiratory centre during asphyxia such as we will discuss later. We have, however, examined two patients in this period in deep coma; one was cyanotic. In each case movement was definitely limited on the affected side. The paresis was so marked in the case showing cyanosis that the affected side of the chest was "sucked in" when expansion occurred on the normal side.

With spasticity such as occurs in long-standing cases of hemiplegia the same results are obtained: a diminution of expansion of the chest on the affected side during quiet breathing, voluntary respiration and hyperpnœa. This probably holds true for other states of rigidity as exemplified by our one case of unilateral Parkinsonism. On the contrary, with muscular hypotonia or flaccidity the amplitude of the respiratory movement is always greater on the affected side. An increase in excursion on the affected side has only previously been described by Jackson for quiet breathing and by Grawitz on his single case of "crossed paralysis." This is true no matter whether the hypotonia occurs with evidence of damage to the motor pathways alone, or sensory pathways or whether a combined motor-sensory loss is found.

It must be mentioned that the increase in movement on the affected side in flaccid hemiplegia is less easily determined on inspection of the chest alone than in the cases of spastic hemiplegia. It occurs late in the act as a "lag" and is best seen in the first and second interspaces. It may be visualized better by standing behind the patient and becomes more apparent on placing the hands over the upper chest and comparing the movements of each hand during inspiration.

Although the observations have been few, the effects of hyperpnœa following inhalation of carbon dioxide, both in cases with spasticity and flaccidity, have shown that the increased depth of respiration persists for a longer period on the hemiplegic side than on the normal. In the cases of spacticity, at the end of the period of hyperpnœa the amplitude on the affected side may be equal to or greater than the normal side while formerly during quiet breathing it was always less. If a voluntary inspiration is taken during the period of hyperpnœa the amplitude of the movement is the same as that of voluntary inspiration during quiet respiration. Two possible explanations have occurred to us. Tone may be decreased during hyperpnœa, but if this is so we could expect an equal increase in amplitude on the normal side. This has never been true. The other is that pathways from the cortex or supramedullary centres which control the activity of the respiratory centre in the medulla have been destroyed and this centre now acts alone and excessively.

Jackson originally suggested the existence of cortical inhibitory pathways because of the fact that quiet breathing was greater on the affected side while voluntary breathing was decreased. Although we have seen only one case showing such dissociation of amplitude between quiet and voluntary respiration movement, it does appear regularly in comparing reflex and voluntary breathing in hyperpnœa. Furthermore, the recent experimental work of Smith [17] and Bucy [4] corroborates the results of many previous workers who have demonstrated that arrest or slowing as well as acceleration of respiration can be produced by electrical stimulation of the cerebral cortex in man and animals.

Most writers have stated that the decrease of movement on the affected side occurs only in voluntary respiration. Nothnagel [13] and Strümpell [19] ascribed this to paralysis of the scalenus anticus muscle and they were later supported by Faschingbauer [6]. Our observation shows that this diminution occurs not only in voluntary respiration but also during quiet breathing. The question arises, are the intercostals paretic alone or is some other factor responsible for this change? That movement occurs, though diminished in spasticity but increased in flaccidity, leads us to assume that the intercostal muscles are not paralysed and that the variables of tone are responsible for the changes in amplitude.

The modifications of phasic reflex activity playing upon a background of tone has been described by Walshe [20] in his studies of the Babinski response in states of paraplegia in extension and paraplegia in flexion following spinal cord injuries. In the former the reaction may be a minimal dorsiflexion and abduction of the toe with dorsiflexion of the ankle and ham-string contraction, or as Walshe puts it, " the condition is one in which a flexion reflex incompletely overcomes a strongly maintained hypertonus in the antagonists." In the latter a flexor or mass reflex may supervene on a similar stimulus. In the first case the limb is spastic in extension and the withdrawal only momentarily overcomes the maintained over-active extensor reflexes, while in the latter this exaggerated antagonism is entirely removed and the movement is carried through to its completion.

Reflex respiration is modified in a similar way. It is apparent that voluntary movement likewise has its pattern changed by the existing tone of the portion of the body upon which it acts. It is difficult to separate the impairment of activity through loss of voluntary control from that caused by spasticity if one studies movements of the limbs. In the case of the thoracic cage we have a series of muscles receiving impulses from both hemispheres. If the efferent fibres from one cortex are totally destroyed, voluntary movement still occurs through ipsilateral impulses. This movement, voluntarily induced, must act on the hypertonic or hypotonic musculature affecting the chest wall. The present study presents graphically evidence of the fact that the manifestations of voluntary activity may be impeded or liberated when acting on a hypertonic or hypotonic musculature respectively.

The problem of spasticity leads one to consider what groups of respiratory muscles are hypertonic; whether the auxiliary muscles alone are concerned, or whether the intercostals are involved. In all our cases with spasticity the pectoralis major has formed a firm contracted mass holding the affected arm close to the chest. In several there was a palpable rigidity in the rectus abdominis on the affected side. An increased rigidity in the shoulder girdle and abdominal muscles alone would probably be capable of decreasing the excursion of the affected chest wall by holding the superior and inferior portions of the cage fixed.

In the absence of this spastic "brake" the movements become excessive. That such an event does occur is shown in our Case 6.

This patient was first seen with a spastic hemiplegia and noted as having a diminished expansion on the affected side. Later he developed a flaccid paralysis after a second cerebral accident and now shows an increased excursion on the affected side.

The interaction of the various muscle groups is still obscure. Hoover [8, 9] and Briscoe [3] have described in detail the actions and integrations of the auxiliary muscles with the intercostals and diaphragm in modifying movements of the chest wall. More detailed study with a clearer knowledge of these normal interactions is necessary to explain fully the changes described here.

SUMMARY.

(1) A method is described of recording with a kymograph the simultaneous movements of both sides of the chest.

(2) These movements have been studied in twenty-one cases, including three normal individuals, one case with a pneumothorax, three cases of early hemiplegia, eight cases of spastic hemiplegia, five cases of flaccid hemiplegia, one case of hemianæsthesia and one case of unilateral Parkinsonism.

(3) Normal respiratory activity and movements induced voluntarily were found always diminished on the affected side in acute hemiplegia and in chronic spastic hemiplegia.

(4) Normal respiratory activity and movements induced voluntarily were found always increased on the affected side in chronic flaccid hemiplegia and in one case of hemianæsthesia.

(5) During hyperpnœa the movements on the affected side are increased out of proportion to those on the normal side. This increase persists longer than on the normal side and is noted in both spastic and flaccid hemiplegia.

(6) In one case of unilateral Parkinsonism both reflex respiration and voluntary respiratory movements were decreased on the affected side.

BIBLIOGRAPHY.

[1] Bergmark, G. "Zur Symptomatologie der cerebrale Lahmungen," *Deutsche Ztschr. f. Nervenheilk.*, 1914, **51**, 61.

[2] Broadbent, W. H. "Theory of Construction of the Nervous System," *Brit. Med. Journ.*, 1875, **1**, 371.

[3] Briscoe, J. C. "The Mechanism of Post-Operative Collapse of the Lungs," *Quart. Journ. Med.*, 1919, **13**, 293.

[4] Bucy, P. C., and Case, T. J. "Cortical Innervation of Respiratory Movements," *Journ. Nerv. and Ment. Dis.*, 1936, **84**, 156.

[5] Dejerine, J. "Semiologie des Affection du Systeme Nerveux," 1914, p. 171.

[6] Faschingbauer, H. "Zur Symptomatologie der Hemiplegie," *Wien Klin. Wchnschr.*, 1920, **33**, 251.

[7] Grawitz, E. "Halbseitige Athmung Störungen bei cerebralen Lähmungen," *Ztschr. f. Kl. Med.*, 1894, **24**, 1.

[8] Hoover, C. F. "Diagnostic Lung Signs," *Arch. Int. Med.*, 1917, **20**, 710.

[9] *Idem.* "The Functions and Integration of the Intercostal Muscles," *Arch. Int. Med.*, 1922, **30**, 1.

[10] Jackson, H. "Superior and Subordinate Centres of the Lowest Level," *Lancet*, 1895, **1**, 476.

[11] Leube, W. "Specielle Diagnose der Inneren Krankheiten," 1895, Bd. **ii**, 213.

[12] Mills, C. K. "The Nervous System and its Diseases," 1899, p. 455.

[13] Nothnagel. "Ziemsen's Handb. d. spez. Path. u. Ther," 1876, Bd. **ii**, 96.

[14] Ortner, N. "Zur Lehre von der gleichseitigen Hemiplegia bei cerebralen Erkrankungen," *Deutsche Med. Wchnschr.*, 1897, 372.!

[15] Oppenheim, H. "Lehrbuch der Nervenkrankenheiten," 11te Aufl., p. 497.

[16] Ross, J. "Treatise on Diseases of the Nervous System," 1881, **ii**, 569.

[17] Smith, W. K. "Alterations of Respiratory Movements Induced by Electrical Stimulations of the Cerebral Cortex of the Dog," *Am. Journ. Physiol.*, 1936, **115**, 261.

[18] Starr, A. "Organic and Functional Nervous Diseases," 1903, p. 487.

[19] Strumpell, A. "Lehrbuch Speciellen Pathologie und Therapie der Inneren Krankheiten," 1889, Bd. **ii**, 368.

[20] Walshe, F. M. R. "Physiologic Significance of Reflex Phenomena in Spastic Paralysis of Lower Limbs," *Brain*, 1919, **37**, 269.

NOTICES OF RECENT PUBLICATIONS.

Handbuch der Neurologie. Herausgegeben von O. BUMKE und O. FOERSTER. Berlin: J. Springer. 1936 and 1937.

The four volumes referred to below complete the System of Neurology which has been compiled under the direction of Professors Bumke and Foerster, who deserve the gratitude and congratulation of neurologists on the successful accomplishment of their enormous task. As a work of reference it will be invaluable; the provision of a general index to the eighteen volumes would, however, make it even more useful.

Band II. *Experimentelle Physiologie.* S. 561, mit 137 Abbildungen. Price RM. 105.

The inclusion of this volume indicates the wide scope on which the "Handbuch" was planned. The physiology and mechanics of muscular activity, the physiology of the vegetative system and the conditioned reflexes are dealt with in addition to the functions of the central nervous system. The most noteworthy chapters are perhaps those on the spinal cord by Brücke, on the brain-stem by Rademaker, and on the physiology of the cerebellum and of the cerebral cortex by Dusser de Barenne, but all contributions to it will be of interest to neurologists. Though written as a symposium of the experimental physiology of the nervous system the volume would have been of greater service to the clinician if it had been planned with more immediate reference to the practical or clinical significance of facts and hypotheses which have resulted from experimental work; it is for instance disappointing to find in Berger's chapter on the physiological accompaniments of psychical activity only a page devoted to electric potentials of the brain, while the reader will search in vain for an account of the nervous control of the bladder and rectum. It seems, too, that a few of the authors were more anxious to present their personal views rather than give a general review such as a book as this demands.

Band III. *Quergestreifte Muskulatur, Rückenmarksnerven, Sensibilität, Elektrodiagnostik.* S. 1128, mit 851 Abbildungen. Price RM. 236.

The first half of this volume is devoted by Foerster to the physiology and functional pathology of the striated muscles. The primary and secondary actions of each muscle, and the mechanism of movement at each joint, are fully described, as well as the effects both in rest and in movement of palsies of the individual muscles. The treatment of muscular paralysis, especially by substitution operations, is included. The chapter is a uniquely comprehensive contribution to an important subject, details of which are often neglected. F. Kramer deals with the symptoms of injury and disease of the somatic nerves and plexuses.

Another short but extremely valuable chapter is contributed by v. Weizsäcker on the examination of sensation. In addition to the methods and principles of examination he analyses the various qualities and functions of sensation, and discusses the physiological and psychological factors which may influence the phenomena that result from sensory disturbances. Altenburger's chapter on electrical diagnosis, including chronaxie and the study of action currents in normal and pathological conditions, extends to 340 pages; the significance of the facts revealed by these methods of electrical investigation are analysed and discussed.

Band XV. *Endokrine Störungen.* S. 469, mit 46 Abbildungen. Price RM. 88.

This volume on disturbance of the ductless glands has been wholly written by A. Jores and M. Nothmann, who have evidently collaborated closely in its production. Some of the chapters, as those on the hypophysis-hypothalamic system and the epiphysis, are of direct concern to the neurologist, but many of the others have only an indirect interest, but the volume will be welcome as an up-to-date exposition of subjects which are assuming more and more importance in all branches of medicine.

Band XVI. *Angeborene, Früh Erworbene und Heredo-Familiäre Erkrankungen.* S. 1172, mit 442 Abbildungen. Price RM. 228.

Probably no more difficult task lies before the author who writes on nervous diseases than to classify and describe the various hereditary and familial affections, for often their pathology and symptoms vary in different families, and many cases fail to fall into classical types. How important the hereditary factor may be in pathogenesis is sometimes disputable, for instance, in this volume progressive muscular atrophy, amyotrophic lateral sclerosis, syringomyelia, paralysis agitans and myasthenia gravis are, contrary perhaps to the experience of most, placed among the hereditary diseases or attributed to hereditary influences. But this is only a matter of arrangement, and the juxtaposition of the myopathies to other affections in which muscular wasting is the most prominent symptom, and of paralysis agitans to hereditary diseases characterized by involuntary movements, certainly makes for convenience. All the hereditary affections are fully described and well illustrated, and, as in the volumes, the numerous references and the extensive bibliographies will be extremely useful. The volume also contains chapters on congenital defects and on affections dating from birth or infancy, as Wohlwill's excellent article on the cerebral hemiplegias, diplegias and allied conditions. Hereditary affections of the eye and ear, which neurologists often meet, are also described.

Précis d'Anatomo-Physiologie Normale et Pathologique du Système Nerveux Central. Par P. MASQUIN et J. O. TRELLES (sous la direction de Jean Lhermitte). Paris: G. Doin et Cie. 1937. Pp. 613, avec 185 figures. Price 165 Fr.

Of the many praiseworthy attempts in recent years to provide the student of neurology with a résumé of the more important facts of anatomy and physiology on which to base clinical study none perhaps has been so pretentious and on the whole so successful as this volume written under the supervision of Professor Lhermitte. Its authors start with the assumption that in the study of the nervous system physiology is inseparable from anatomy, while a knowledge of the phylogenetic evolution of structure is often necessary for the proper comprehension of function. Consequently they introduce the chapters on each division of the nervous system by a short sketch of its ontogeny, and often refer to its comparative development; its anatomy and connections are then described and its main functions and the effects of their disturbances are discussed. On the whole this method has yielded excellent results and has furnished the student with an adequate foundation for clinical work, but, as is perhaps inevitable in such a task, the authors have in many cases failed to hold fairly the balance between condensation and completeness, more particularly in the matter of exclusion or introduction of discussions on function, but in this question there is obviously room for diverse opinions. There can be no doubt, however, on the success which the authors have achieved, or on the utility of this book. Some of the diagrams are open to adverse criticism; many are so crude and so unlike the structures they represent that the student may have difficulty in transferring what he learns from them to the anatomy he already knows or studies, and yet many are not so clear as to justify the simplification which is attempted. The extensive use of eponymous terms, always popular in France, is another drawback for the English reader, but the provision of an excellent index is a praiseworthy feature of the volume.

Études sur le Spina Bifida. Par J. LEVEUF (avec la collaboration de I. BERTRAND et H. STERNBERG). Paris: Masson et Cie. 1937. Pp. 330, avec 176 figures. Price 75 Fr.

This volume may safely claim to become a classic in the literature of spina bifida and allied conditions. It is comprehensive yet concise, clearly written and admirably illustrated. The developmental errors to which spina bifida is due are dealt with by Dr. Sternberg of Vienna, and Dr. Bertrand describes the malformations of the brain and cord often associated with it, but the main part is written by Professor Leveuf, who gives in an appendix records of eighty cases which he has observed.

The more important features of the volume are a careful study of the meninges in spina bifida, which enables him to trace the neuro-ectodermal origin of the pia-arachnoid, and the descriptions of mild forms of meningocele which are related to the fully developed forms of the condition. Ætiological factors, in which syphilis is regarded as important, and the various complications are fully discussed. The treatment of spina bifida and the immediate and later results of operation are also dealt with on the basis of the author's large personal experience. The publishers deserve congratulation on the excellent reproduction of the illustrations.

Lehrbuch der Nervenkrankheiten. VON R. BING. 5te Aufl. Berlin: Urban und Schwarzenberg. 1937. S. 618, mit 207 Abbildungen. Price RM. 25.

After an interval of less than five years the author of this useful textbook was called on to provide a new edition, which appears in essentially the same form, but with an addition of 50 pages which are distributed over several of the chapters. The book still preserves its predominantly clinical character, but due attention is given to the pathogenesis and morbid anatomy of disease and to the origin and significance of symptoms. To students and practitioners who read German it can be strongly recommended; to others an English translation of this edition would be welcome.

Les Maladies Nerveuses. Par A. VAN GEHUCHTEN. 4me Édition. Louvain: Libraire Universitaire. 1936. Pp. 718.

The fourth edition of van Gehuchten's textbook has been brought up to date and enlarged by his son and successor, but the general plan is that of the original author. It is claimed to be a simple and practical presentation of clinical neurology with adequate reference to pathology, and such it is. There are numerous illustrations, but unfortunately many are not well chosen or satisfactorily reproduced.

Le Tonus des Muscles Striés. Par G. MARINESCO, N. JONESCO-SISESTI, O. SAGER et A. KREINDLER. Preface de Sir Charles Sherrington. Imprimerie Nationale, Bucarest. 1937. Pp. 355.

A short but delightful preface from the pen of Sir Charles Sherrington introduces this comprehensive and valuable monograph. It opens with a critical review of all the experimental data now available upon the problem of skeletal muscle tonus, and thus gathers together a vast mass of information in concise and lucid manner. The application of this knowledge to the clinical study of motor disorders, and the additions thereto which clinical investigation has made possible are then fully described. The symptom-complexes of pyramidal and extrapyramidal disorders are analysed on physiological principles, utilizing the work of Sherrington, of the Utrecht school and of Lapicque.

Much original work of the authors is also included. This is the first satisfactory approach to a synthesis of the experimental and clinical work upon the problem of muscular tonus, and it may be warmly commended to all who are interested in this problem.

Die Hirnkammerformen bei Hirntumoren. VON OTTO DYES. Leipzig: G. Thieme. 1937. S. 79, mit 105 Abbildungen. Price RM. 16.

This monograph on the interpretation of encephalograms in cases of cerebral tumour is so profusely illustrated that it may be described as an atlas. The 105 figures which it contains will, apart from the text, be found extremely useful, and the discussions on the reading of films and the significance of details, many often lost sight of, adds to its value. The numerous radiograms are excellently reproduced.

Abcès subaigus et chroniques des hémisphères cérébraux : Sur une méthode de traitement. Par CLOVIS VINCENT, MARCEL DAVID et HARDEN ASKENASY. Paris: Masson et Cie. 1937. Pp. 46.

The authors describe a method they have employed successfully in the treatment of chronic or subacute cerebral abscess. The method of choice, when the abscess wall is sufficiently thick, is the ablation of the entire abscess with its surrounding brain. When this is not immediately possible a preliminary decompression over the abscess is performed, leaving the dura intact. A suitable moment for ablation is then awaited, and pending it aspiration of the abscess may be necessary.

Over de Diagnostiek van Het Meningioma Cerebri. door A. C. DE VET. Scheltema and Holkema, Amsterdam. 1936.

In this University Thesis the author records the analysis of the history and symptoms of a series of thirty-eight cases of cerebral endothelioma, undertaken to discover if possible any indications by which a pathological diagnosis of the nature of the growth can be made clinically, and for the guidance of the surgeon.

He finds no constantly present or pathognomonic sign by which the presence of an endothelioma can be ascertained before operation. Nevertheless a number of interesting points emerge from the study. When "irritative" symptoms, i.e. Jacksonian attacks, occur in cases of parasagittal endothelioma, the cortical point of origin of the attack as revealed by its form is likely to be related to the periphery rather than to the centre of the growth as this is viewed from the surface. Homolateral paresis and reflex changes are occasionally seen and are presumably due to pressure of the edge of the tentorium upon the laterally displaced cerebral peduncle, as originally described by Kernohan and Woltman. This "false localizing sign" seems commonly associated with frontal endothelioma. Another common feature of endothelioma is a fluctuation of symptoms in its clinical course.

Radiological examination frequently reveals either rarefaction or thickening of the skull overlying an endothelioma. The various appearances in the latter case are described. The presence of calcification in the tumour substance was exceptional. Ventriculography was of no considerable assistance, and is in the author's view to be avoided when adequate localizing information can be otherwise obtained.

Études Neurologiques. Par G. GUILLAIN et P. MOLLARET. Paris: Masson et Cie. 1936. Pp. 300. Price 60 Fr.

The present is the seventh volume of the series. It contains a lengthy study of Friedreich's Ataxy, with particular reference to the bulbo-cardiac syndrome which frequently heralds a fatal termination of the malady. Other chapters deal with the myoclonic syndrome and with a variety of neuropathological problems.

The material is presented in the attractive and lucid manner which readers of the series have learned to expect.

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To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

SEPTEMBER, 1937

BRAIN.

PART 3, VOL. 60.

VASOMOTOR RESPONSES IN THE TOES: EFFECT OF LESIONS OF THE CAUDA EQUINA.[1]

BY J. DOUPE (WINNIPEG), J. S. M. ROBERTSON (GLASGOW)
AND E. ARNOLD CARMICHAEL.

WHEN determining the character of vasomotor responses in the digits of man, it was observed that it was more easy to obtain these responses from the toes than the fingers. This observation was considered worthy of further investigation and it is the purpose of this paper to describe the methods used and to discuss the results obtained.

METHOD.

A series of eight normal subjects were submitted to the following investigations: While the subject lay covered with blankets in a quiet and draught-free room, continuous volume records of the two large toes and of a finger were taken by means of suitable plethysmographs and recorded photographically (Bolton, Carmichael and Stürup, 1936). Throughout the observations care was taken to ensure that the toes and fingers were at the same level above the heart—usually 5 cm. above the level of the sternum. One limb, commonly the left upper limb, was immersed and kept gently moving in a tank of water at 44° to 45° C. This produced a rise in rectal temperature which was recorded every fifteen seconds by means of a thermojunction situated 5 cm. above the anal sphincter; it also produced and sustained a widespread dilatation of the cutaneous blood-vessels of the digits of the feet and hands. During this state of peripheral vasodilatation, different stimuli were given, such as multiple and single pin-pricks, touch and cold, to various parts of the body; the subjects were also periodically requested to take a deep breath. It has been shown that following such stimuli there is a diminution of digit volume which results from vasoconstriction of the peripheral blood-vessels (Uprus, Gaylor, Williams and Carmichael, 1935). Other forms of stimuli were given, which will be considered in detail in the text. In order to determine the behaviour of the digit volume without any known stimuli being given, records were obtained during long periods without disturbance. Four subjects suffering from a lesion of the cauda equina were similarly investigated by these methods.

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[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Doupe held a Halley-Stewart Research Fellowship.

RESULTS.

Normal.—Once a steady state of peripheral vasodilatation had resulted from warming the indifferent limb, it was observed that without any known stimulus synchronous diminutions in the volume of the large toe occurred at frequent intervals. As these changes took place without the provocation of any given stimulus, they will be referred to hereafter as "spontaneous." When these "spontaneous" volume changes occurred, it was seldom that any concurrent changes took place in the finger.

A study was made of the changes in digit volume resulting from a variety of stimuli. In a large series of stimuli such as single or multiple pin-pricks to the arm, it was found that a light stimulus not infrequently resulted in a diminution in volume limited to the toes only. This, however, could not be produced with any regularity. Other stimuli, such as cold, touch, distension of the rectum and testicular pressure, gave similar results. To demonstrate these observations graphically, the following methods have been used. The amount of diminution in volume as seen in the photographic records has been measured in centimetres, by measuring the amount of volume changes from a diastolic phase of pulse beat before to a diastolic phase at the greatest change of volume (fig. 1). If in a record of volume changes occurring in a toe and a finger, the amount of vaso-constriction in each was measured as above and these amounts were then plotted against each other, it was possible to obtain a chart (fig. 2). Utilizing such a method of plotting the results it was possible to obtain a chart (figs. 3A and 4A) which indicated the amount of diminution in volume of one digit compared with that of another following upon a large number of stimuli given in the course of one experiment. A study of such a chart showed that the volume of the toes frequently diminished without that of the finger and when the finger did change in volume that the

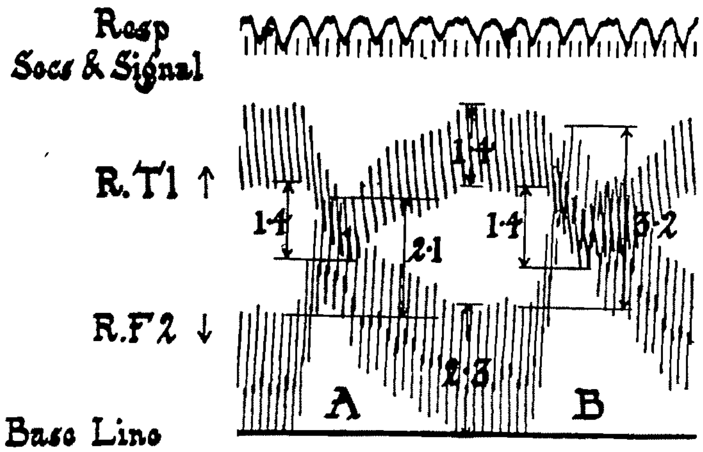

FIG. 1.—Record of volume of right large toe (R.T.1) and right index finger (R.F.2) Arrows point in direction of increase of volume. To first stimulus R.T.1 has diminished 1·4 cm. and R.F.2, 2·1 cm. To second stimulus R.T.1 has diminished 1·4 cm. and R.F.2, 3·2 cm. Size of R.T.1 pulse wave, 1·4 cm. and of R.T.2, 2·3 cm.

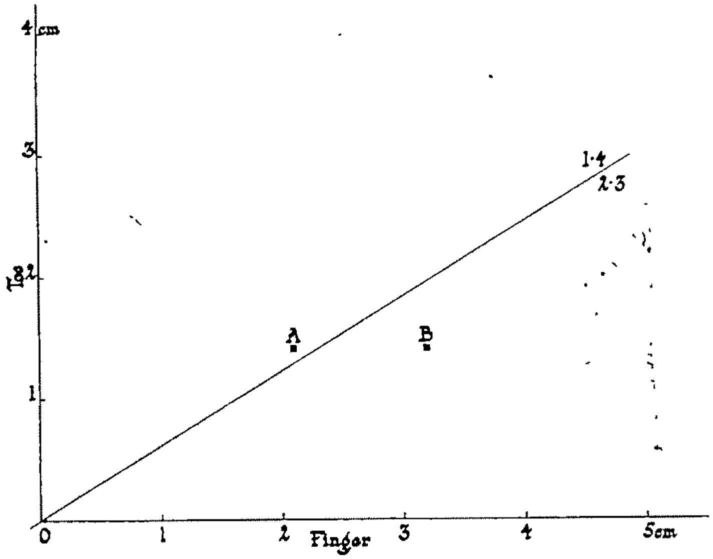

FIG. 2.—Points A and B are plotted from the figures given in fig. 1. The line is given by ratio of size of pulse wave of R.T.1 (1·4 cm.) to size of pulse wave of R.F.2 (2·3 cm.). Abscissa represents the amount of vasoconstriction in toe; ordinate represents amount of vasoconstriction in finger.

change in the toe volume was generally greater in degree than that of the finger.

It was possible that this difference in volume changes, which have previously been shown to be the result of vasoconstriction, might be explained by the fact that there were more blood-vessels in the toe than in the finger. Such a possibility was investigated in two ways. First,

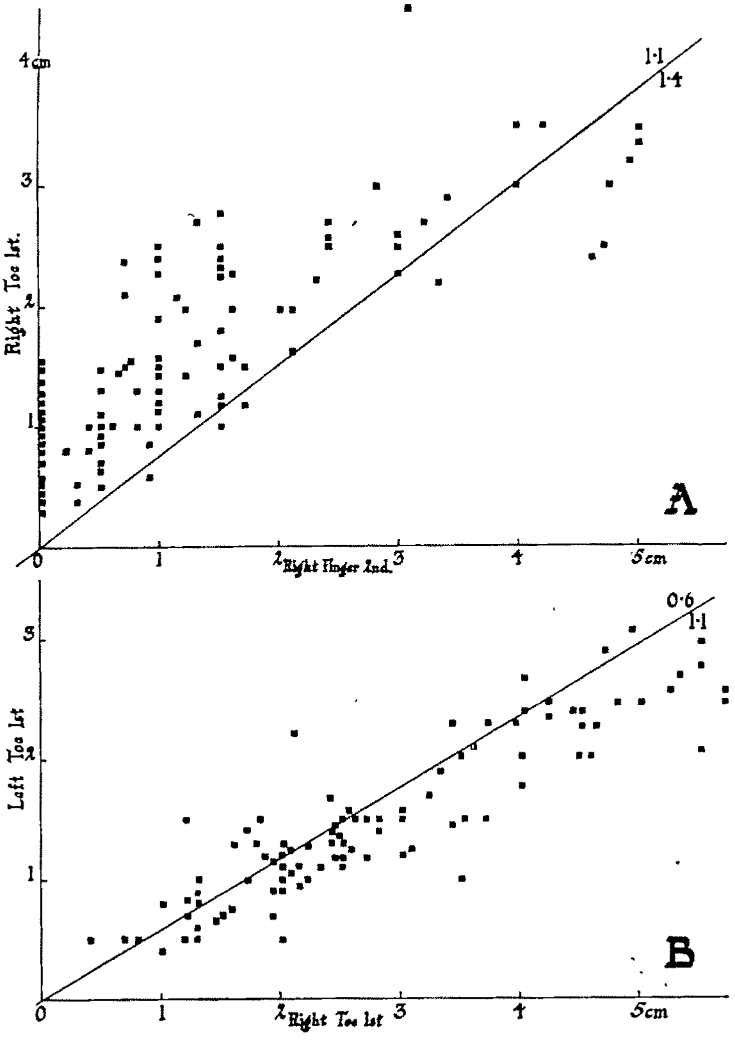

Fig. 3.—Normal. A, Abscissa represents amount of vaso-constriction in the toe, ordinate the amount of vasoconstriction in the finger. The line is obtained by the ratio of size of pulse wave of right large toe (1·1 cm.) to size of pulse wave of right index finger (1·4 cm.). Each point indicates the amount of vasoconstriction in the toe against that in the finger, resulting from a given stimulus. B, Similar, except that the right large toe is plotted against the left large toe.

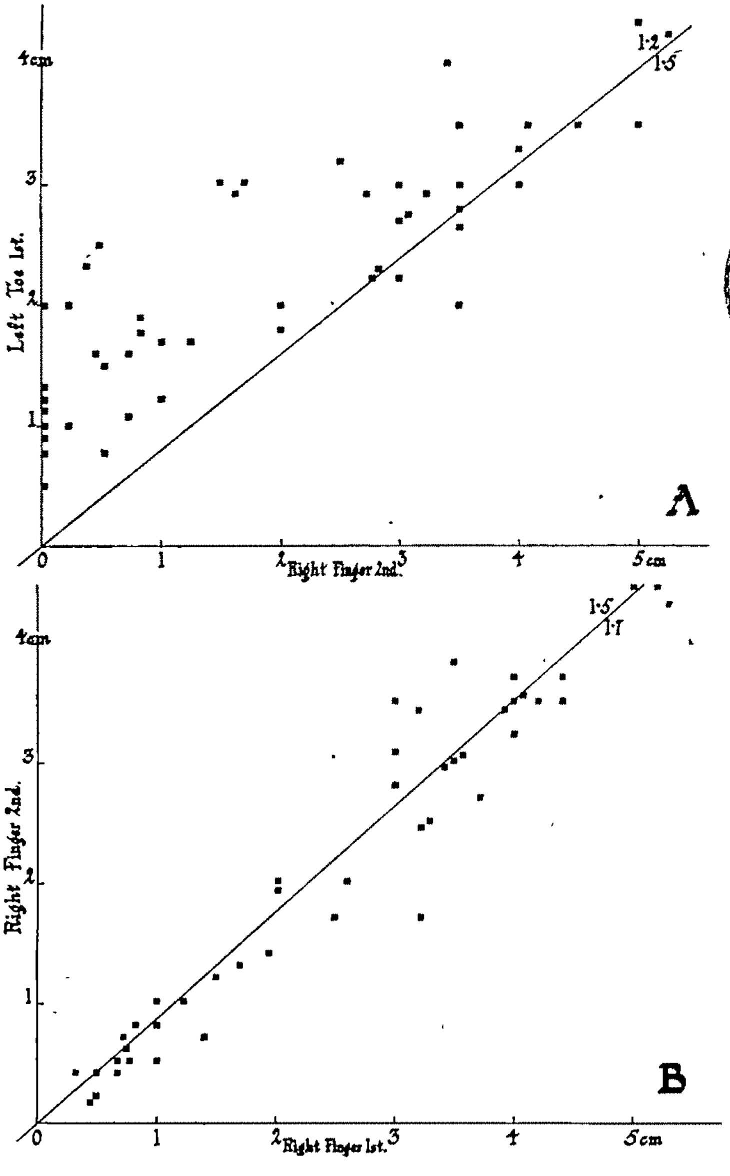

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FIG. 4.—Normal. A, Chart obtained by plotting amount of vasoconstriction in the left large toe against that of right index finger. B, Chart obtained by plotting amount of vasoconstriction of right index finger against that of right thumb.

it was determined that there was a close relationship between the vasoconstriction in a digit and the size of pulse wave as recorded in the records. Thus, if the amount of vasoconstriction in one toe was plotted against that in the other toe, the points so obtained were found to lie in close relationship to a line given by the ratio of the size of pulse wave of the one toe to that of the other (fig. 3B). Again, if the amounts of vasoconstriction occurring in the thumb, a digit more similar in size to the toe, were plotted against those from a finger, a linear relationship was again obtained which was closely related to that given by the ratio of size of pulse wave of thumb to that of finger (fig. 4B). As there was such a close relationship between the amounts of vasoconstriction occurring in the large toes of the two feet and again between those of the thumb and index finger, it appeared that the greater vasoconstriction in the toe was not explicable by a greater number of blood-vessels in the toe. Now if on the chart obtained by plotting the size of volume changes in the toe against those of the finger a line given by the ratio of the size of pulse wave in the toe to that of the finger was drawn, the points were found to lie in the area on the side of the line favouring the toe (figs. 3A and 4A). By this method it was possible to demonstrate that in healthy subjects greater changes occurred in the toe volume as compared with the finger volume when known stimuli were given, and secondly, that the toe frequently altered in volume without a similar change in the finger. These results indicate that a greater degree of vasoconstriction occurred in the vessels of the toe than in those of the finger when a variety of sensory stimuli were given.

Sympathectomized limb.—In one subject who had the left lumbar sympathetic chain removed two years previously for a condition other than vascular disease, a similar series of observations was made. It was noticed that many "spontaneous" waves of diminution of toe volume occurred in the toe of the non-sympathectomized leg, but never in that of the sympathectomized toe. Thus it may be deduced that the "spontaneous" waves of diminution in toe volume are dependent upon the integrity of the postganglionic fibres; in other words, that the "spontaneous" diminution in toe volume is an indication of vasoconstriction. Similarly it was found that following stimuli a diminution in volume of the normally innervated toe occurred, but not in the sympathectomized toe. This is confirmatory evidence that the changes in volume following stimuli are the result of active vasoconstriction.

If from the records obtained from such a subject, a chart be plotted as before, it will be found that vasoconstriction occurs more readily in the non-sympathectomized toe than in the finger and that if the responses in the sympathectomized toe be plotted againt those of the healthy toe, the points lie along the base line of the healthy toe, as would be expected from the above observations (fig. 5A and B).

Attempts were then made to find a stimulus which readily gave responses limited to the toes.

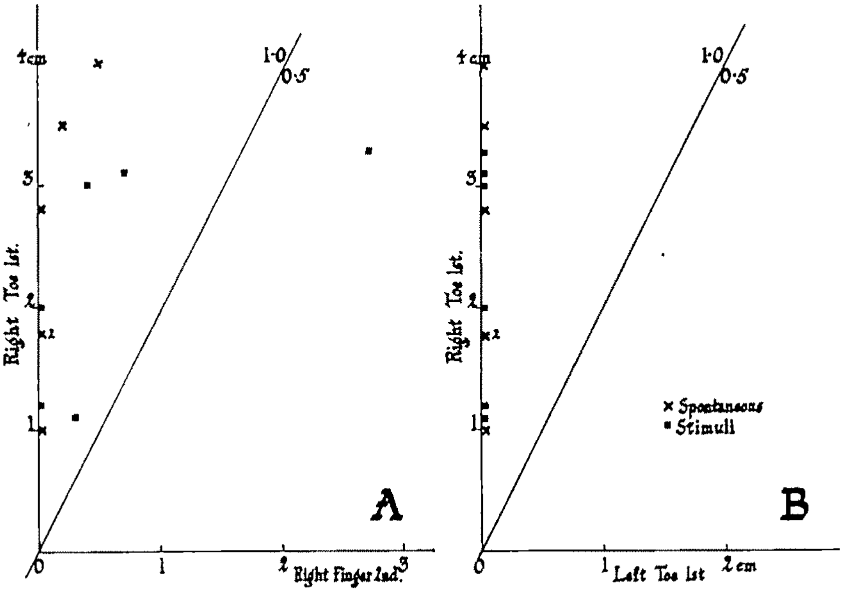

FIG. 5.—Left lumbar sympathectomy. A, Amount of vasoconstriction in right large toe plotted against that of right index finger. B, Amount of vasoconstriction in right large toe plotted against that of left large toe.

Sensory stimulus. The site and nature.—The following observations were carried out to determine the first point. The degree and site of the stimulus were varied and the results compared. For instance, pin-prick was used as the stimulus: the degree was varied in two ways, either by increasing the weight of the pin or by the number of pin-pricks. It was found that if the stimulus was a slight single pin-prick, vasoconstriction tended to be greater in the toes than in the fingers; on the other hand, a heavy stimulus of multiple heavy pin-pricks resulted in a maximal constriction of the vessels of the toes and fingers. Secondly, it was observed that with stimuli to the leg, relatively greater vasoconstriction occurred in the toes than when similar stimuli were given to the arm. Irrespective of the site of the stimulus it was a comparatively rare event that vasoconstriction limited to the toes occurred.

The results of a great variety of stimuli were also investigated, including cold to the skin, distension of the rectum, pressure on the abdomen or soles of the feet and testicular pressure, but with none of these was it possible to obtain responses limited to the toes with any regularity, though as reported before, minimal stimuli tended to result in greater constriction of the toe blood vessels.

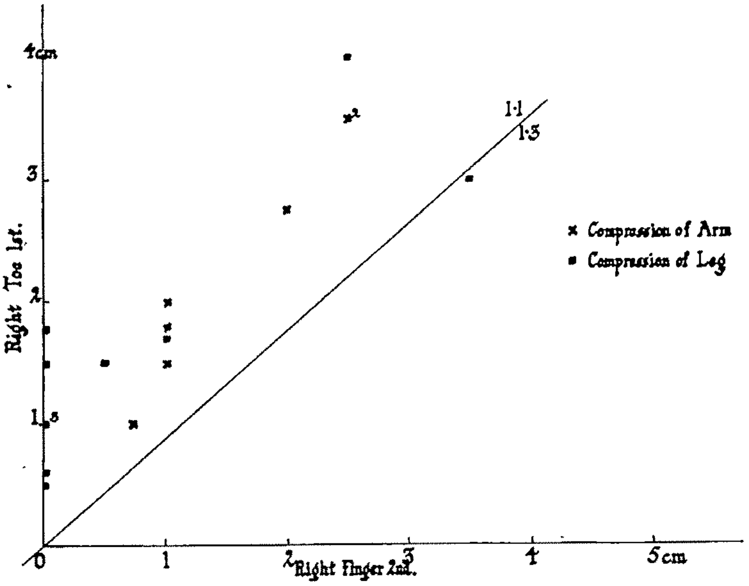

FIG. 6.—Normal. Amount of vasoconstriction in right large toe plotted against that of right index finger.

Attempts were then made to alter the circulation in one lower limb in four normal subjects. This was carried out by the rapid distension of the cuff of a sphygmomanometer placed around the calf of one leg and held for a few seconds; the cuff was blown up to pressures varying from 10 to 200 mm. Hg. With the lower ranges of pressure it was assumed that a degree of venous engorgement would result while with the higher pressures occlusion of the circulation would follow. Following such proceedings, these observations were made. With pressures varying between 30 and 80 mm. Hg. it was possible to produce vasoconstriction limited to the other toe. Owing to the alteration produced by the venous engorgement on the same side, no satisfactory records could be obtained by the plethysmographic methods of the changes in the vascular bed due to vasoconstriction of the vessels of the toe on the side on which the bag was blown up. In three of the normal subjects vasoconstriction limited to the toes was produced with greater ease than with all other forms of stimuli. Again, if the cuff, instead of being blown up rapidly, was inflated slowly, it was only when a pressure of 30 to 50 mm. Hg. was reached that the vasoconstriction occurred in the other toe. This suggested that the critical pressure was in the region of 30 to 50 mm. Hg. and it was observed that at this pressure evidence of commencement of venous engorgement was most apparent. In three subjects, a comparison of the results of the effect of cuff pressure in the leg with those from cuff pressure in the arm were made. In one subject the cuff pressure in the leg produced many responses limited to the other toe, while similar cuff pressure in the arm resulted in responses in both toes and the fingers of the other hand (fig. 6). In the other two subjects the results which were obtained, though pointing in the same direction, were less demonstrative.

From these observations it appeared that light constriction of the leg resulted in greater vasoconstriction in the toes than in the fingers, and on many occasions vasoconstriction limited to the toes. As touch or local pressure had not so consistently given similar results, it was believed that the venous engorgement from the constriction of the bag was the cause of the vasoconstriction.

Other methods of producing venous engorgement were tried, such as hanging one leg dependent from the knee, but the movement of the leg was in itself found sufficient to produce a vasoconstriction in the finger as well as in the toe; it was thus not possible to determine by other methods if, in fact, the state of venous engorgement was the best stimulus for the production of vasoconstriction limited to the toes.

Lesions of the cauda equina.—A survey was then made of the responses obtained from four subjects suffering from the effects of a lesion of the cauda equina.

In subject A the lesion was in the nature of a fracture dislocation of the lumbar spine with a sensory loss over the segments from lumbar 2 downwards on the left side and from lumbar 3 downwards on the right side. Three subjects suffered from tumours localized to the cauda region: In B the sensory disturbance was limited to the sacral segments, 2, 3, 4 and 5; in C to lumbar 4 and 5, and sacral 1, 2, 3, 4 and 5 segments; and in D to lumbar 5 and sacral 1, 2, 3, 4 and 5 segments. Three of these subjects were not completely bed-ridden.

These lesions, being situated within the vertebral canal, had severed the lower lumbar and sacral anterior and posterior roots. As the upper lumbar and lower dorsal roots were not involved in the lesion, the vasomotor preganglionic fibres destined to supply the toes were intact.

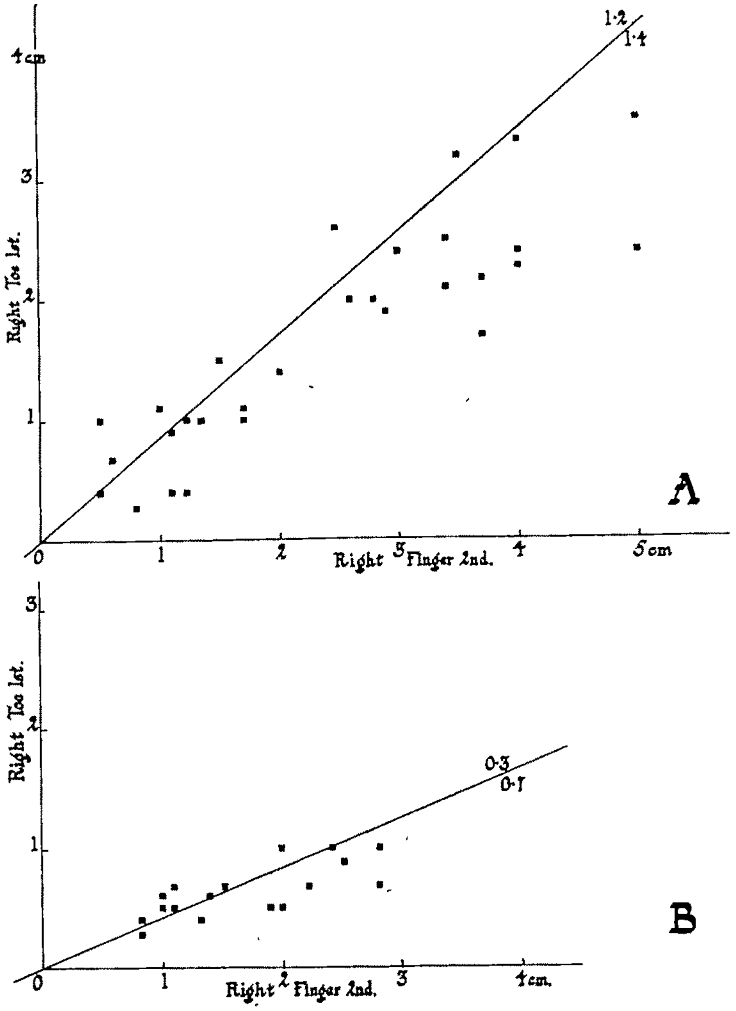

FIG. 7.—Cauda equina lesion. A, Amount of vasoconstriction in right large toe plotted against that in right index finger from Subject C. B, As above for subject A.

These subjects, therefore, were ideal for studying vasomotor responses in a digit deprived of its afferent connections with the spinal cord. When these subjects, on more than one occasion, were subjected to the procedure outlined at the beginning, it was found that in three (A, C and D) no "spontaneous" vasoconstrictions occurred in the toes over periods of seventy minutes, eighty minutes and sixty minutes respectively. During these periods stimuli of varying degree were given at intervals, and when the measurements of the resulting vasoconstriction in the toe and finger were charted as before, it was found that the points lay along the line given by the ratio of pulse wave sizes (figs. 7A and B). A study of these charts showed that the vessels of the toes constricted neither spontaneously nor more than those of the finger, even when minimal stimuli were given. In subject B, who had only the lower sacral roots involved by the lesion, the toe vessels were found to constrict spontaneously on several occasions and when the responses to stimuli were charted, the results pointed to the toe vessels constricting better than the finger vessels.

It appeared, therefore, that when the afferent fibres from the legs were cut, no "spontaneous" responses occurred in the toe vessels, and that to stimuli the constriction of the toe vessels was no greater than that of the finger vessels. As the subject with involvement of the sacral roots alone did not show this, it was deduced that the afferent fibres most concerned with the production of "spontaneous" toe vasoconstriction were those of the lower lumbar and first sacral roots. These observations further suggested that the afferent impulses arising in the leg influence the vasomotor responses of the toe vessels.

DISCUSSION.

From the results obtained and recorded it is apparent that the blood-vessels of the toes in a normal subject are more susceptible to constrictor influences than the vessels of the fingers, and as a result constrict more readily than those of the fingers. As in the subjects with a lesion of the cauda equina "spontaneous" constriction of the toe vessels did not occur it is probable, therefore, that the "spontaneous" vasoconstrictions result from afferent impulses from the legs. Again, in the absence of afferent impulses from the legs, the blood-vessels of the toes no longer constrict more readily than those of the finger. This observation suggests that in the normal there is a constant bombardment from the legs of reflex centres within the central nervous system dealing with vasoconstriction of the toes and that when an added impulse is sent in, these centres respond more readily than those controlling the vessels of the fingers. As the blood-vessels of the toes appeared to be fully dilated by the procedure of warming the body, it is probable that the constant bombardment by impulses from the legs, as postulated, is insufficient by itself to produce a degree of vasoconstriction.

Regarding the nature of the stimulus which provokes the "spontaneous" constriction of the toe vessels, the observations dealing with venous engorgement appear pertinent, for the engorgement of the venous bed of one leg frequently produced vasoconstriction limited to the other leg. It has not been possible to determine if the stimulus arises from the veins, surrounding tissues, or capillaries. Other stimuli may also produce this phenomenon, but, whatever their nature, they apparently arise from the legs, as no "spontaneous" constriction occurred when the legs were insensitive. This local effect of venous engorgement of the legs may play a part in the regulation of the circulation on adopting the erect posture.

SUMMARY.

Evidence has been produced to show that in a normal subject the toe vessels constrict following a stimulus more readily than the finger vessels; that this state of the toe vessels results from afferent impulses from the legs and that these afferent impulses alone are insufficient to produce constriction of the toe vessels.

It is a pleasure to record our thanks to the Honorary Staff of the National Hospital for kindly permitting the study of patients admitted under their care.

REFERENCES.

BOLTON, B., CARMICHAEL, E. ARNOLD, and STÜRUP, G. *Journ. Physiol.*, 1936, **86**, i, 83.

UPRUS, V., GAYLOR, J. B., WILLIAMS, D. J., and CARMICHAEL, E. ARNOLD. *Brain*, 1935, **58**, 448.

DURAL SINUS THROMBOSIS IN EARLY LIFE: RECOVERY FROM ACUTE THROMBOSIS OF THE SUPERIOR LONGITUDINAL SINUS AND ITS RELATION TO CERTAIN ACQUIRED CEREBRAL LESIONS IN CHILDHOOD.[1]

BY ORVILLE T. BAILEY AND GEORGE M. HASS.

THE present study is devoted to a description of three cases which survived acute attacks of thrombosis of the superior longitudinal sinus and to an evaluation of the anatomical lesions in relation to certain acquired types of cerebral degeneration and deficiency in childhood.

The frequent occurrence of recovery from thrombosis of one or both lateral sinuses has long been recognized. Experience with lateral sinus thrombosis secondary to mastoiditis has shown clearly that many patients recover, although surgical approach to the sinus is not attempted. Thrombosis of the superior longitudinal sinus is usually considered to be an invariably fatal process in itself, or as an incident in the terminal stages of various diseases, but Byers and Hass [2] have shown that the cerebral lesions often are not sufficiently severe to cause death.

Although it seems to these authors that certain patients with sinus thrombosis and consequent cerebral injury might recover, they had no definite pathological proof. Since their report, a careful search of the dural sinuses has been made in every patient with a cerebral defect detected at necropsy, and we have been able to find three patients with organized thrombi in the dural sinuses. In studying the histories of these patients it was found that each had developed normally to the time of an acute illness. In two instances the illness was accompanied by neurological symptoms; in one it was without such manifestations. The illness was followed in each instance by progressive mental deterioration. At necropsy organized and canalized thrombi were found in the superior longitudinal sinus. All patients showed different forms of cerebral injury. The lesions, in our opinion, could be regarded as a result of attempted repair of pathological changes known to be associated with thrombosis of the superior longitudinal sinus. The detailed reports follow:—

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[1] From the Department of Pathology of the Harvard Medical School and the Laboratories of Pathology of the Children's and Infants' Hospitals and the Peter Bent Brigham Hospital, Boston, Mass.

Case 1.—The patient, R. S., was a 6-year-old boy who came to the hospital because of difficulty in breathing and swelling of the legs. One month before admission the patient developed an upper respiratory infection. Cardiac failure set in rapidly, and admission to hospital was advised. On admission there were typical physical signs of mitral stenosis. The patient was bright, active and co-operative. There were no abnormal neurological findings. He was discharged six weeks after admission in fairly good condition. Three and a half months later the patient developed an acute bronchitis which was followed by right otitis media. *Streptococcus hæmolyticus* was cultured from the throat. One week before the second admission the temperature rose to 101° F., with reappearance of sore throat. On the day before admission examination showed that all tendon reflexes were diminished, while the cremasteric responses were active. Kernig's and Babinski's signs were not elicited. The pupils were normal. There was definite papillœdema. Roentgenograms showed evidence of increased intracranial pressure. Lumbar puncture yielded clear fluid containing ten red blood-cells and four white blood-cells per c.mm. Pandy's test was negative. On the day of readmission, the temperature was 102° F. The child was dull and apathetic. The right pupil was smaller than the left; both reacted sluggishly to light. There was marked bilateral papillœdema. All tendon reflexes were diminished. Babinski's sign could not be elicited. There was marked rigidity of the neck. Spinal fluid obtained by lumbar puncture was clear. The pressure was 230 to 250 mm. of water. The globulin test was negative; the sugar was 60 mg. per cent.; the total protein 30 mg. per cent. Microscopical examination showed 200 red blood-cells and 30 white blood-cells per c.mm. Cultures of the cerebrospinal fluid were sterile. For several days the patient continued to have marked evidence of meningeal irritation and increased intracranial pressure. Increasing dilatation of the veins of the scalp was noted on the right. Xanthochromic fluid was obtained from the subarachnoid space, while both ventricular and lumbar fluids were clear. Five days after admission the margin of the left optic disc was completely obliterated, while there were two diopters of choking of the right disc. The boy became so irritable that it was difficult to estimate his mental reactions, but the impression was gained that there was a progressive impairment of intelligence. No localizing signs of neurological disturbance developed. The papillœdema receded during the following month, but it never wholly disappeared. The neurological and mental conditions remained unchanged, but the physical condition became progressively worse. Intractable œdema developed and death occurred suddenly five months after onset of the acute pharyngitis and otitis media.

Autopsy.—There was no evidence of subacute bacterial endocarditis, and culture of blood from the heart showed no growth.

The brain weighed 1236 grams (normal weight at this age, 1275 grams) [3]. There was a large amount of yellowish gelatinous fluid in the subarachnoid space over the entire convexity of the brain. On exploration of the venous sinuses, an adherent thrombus was found in the superior longitudinal sinus, which extended along its middle and posterior thirds. Similar adherent thrombi were found in the torcular Herophili and the right lateral sinus as far as the region of the right sigmoid sinus. At no point could complete occlusion of any of the sinuses be demonstrated. The thrombi were greyish-white in colour and were so fused with the sinus wall that they could not be pulled away. The openings of the middle and posterior group of right superior cerebral veins were obstructed by the thrombus in the longitudinal sinus, but apparently there had been no extension of the thrombus into these vessels. The tympanic antra and the mastoid air cells were free from exudate and necrosis of bone. The tympanic membranes were intact. The meninges of the spinal cord were not unusual. Transverse sections revealed no evidence of softening or gliosis of the spinal cord.

After fixation in formalin the brain was cut in coronal sections at 10 mm. intervals. There was one small zone (4 by 5 mm.) in which the grey matter of the cerebral cortex was replaced by soft brown material; this was located 2 cm. lateral to the superior longitudinal sinus in the posterior portion of the right superior frontal gyrus. No other areas of softening or hæmorrhage were encountered. The lateral ventricles, while symmetrical, were moderately dilated. The subependymal vessels were unusually prominent. There was no occlusion of the aqueduct of Sylvius or of the foramina of Munro.

Microscopical examination.—Sections from the superior longitudinal and right lateral sinuses showed organized and canalized thrombi which occupied about one-half the lumen of each sinus. Thus, there was a continuous patent venous channel of reduced size. The surface of the thrombi adjacent to the lumen was covered by a single layer of flattened endothelial cells. Beneath these, there was a large amount of fibrous tissue made up of irregularly placed fibroblasts separated by parallel bands of refractile collagen fibres. Near the sinus wall the connective tissue was looser in texture and pierced with numerous loose-meshed blood-containing spaces. In this region many phagocytes containing hæmosiderin were found. Nearer the sinus wall there were occasional capillaries with well-developed endothelium and refractile basement membranes. No evidence of recent thrombosis was found. The walls of both the superior longitudinal sinus and the right lateral sinus, except in the region of the thrombi, were normal in structure. A very small number of phagocytic cells containing hæmosiderin were found from place to place among the connective tissue fibres of the adjacent dura.

The area of discoloration in the right superior frontal gyrus proved to be a zone of old hæmorrhage and softening. The central portion contained no normal tissue, but was occupied by loosely arranged compound granular corpuscles, some of them containing clear vacuoles and others filled with hæmosiderin. Numerous small capillaries extended into this region from the leptomeninges, and occasionally delicate strands of collagen accompanied them. About the edges of the lesion there were numerous astrocytes, some of them of the giant and binucleate types. Compound granular corpuscles were present, but were less numerous at the margins than they were at the centre of the lesion. Adjacent to the zone of astrocytosis there was normal cortical tissue. The leptomeninges over the lesion were increased in vascularity and there were cells in the subarachnoid space containing hæmosiderin. In nearly all sections the leptomeningeal vessels were dilated and surrounded by a few hæmosiderin-laden phagocytes. The brain was otherwise normal.

Comment.—This patient presents an interesting problem in diagnosis. Any diagnosis must account for: First, an increase in intracranial tension and stiffness of the neck in a patient with severe rheumatic heart disease, acute pharyngitis and otitis media; secondly, the development over a period of five months of mental deterioration without localizing neurological signs; thirdly dilatation of scalp veins and persistence of an increased intracranial tension; fourthly, evidence of hæmorrhage into the subarachnoid space; and finally the absence of demonstrable infection of the meninges.

At necropsy there were three significant findings: First, a mural thrombus in the right auricle of the heart; secondly, a small area of old hæmorrhage and softening in the cortex of the right superior frontal gyrus and organizing hæmorrhages in the overlying and adjacent pia-arachnoid; thirdly, an organized and canalized thrombus partially obstructing the right lateral sinus, the torcular Herophili and the posterior two-thirds of the superior longitudinal sinus.

It is possible that the area of softening and hæmorrhage in the cerebral cortex is an organizing infarct secondary to an embolus from a thrombus in the heart. Although no thrombi were found at necropsy in the left auricle or left ventricle of the heart, they may have been present at one time. This possibility is favoured by the fact that thrombi were found in the right auricle. If it is assumed that a cerebral infarct was the primary lesion, it is conceivable that thrombi originating in the zone of necrosis may have extended into the superior longitudinal sinus and initiated an extensive thrombosis of the dural sinuses.

An entirely different interpretation may be made, if the right otitis media is considered to be the primary lesion. This interpretation depends upon a well-recognized sequence, namely, otitis media (with or without mastoiditis), lateral sinus thrombosis, retrograde propagation of the thrombus into the superior longitudinal sinus and obstruction of the tributary cerebral veins in such a way as to produce hæmorrhages and necrosis in the brain. We believe that the clinical and pathological data may be explained best by this interpretation.

Whatever interpretation is placed on this case as a whole, it serves to emphasize that thrombosis of the superior longitudinal sinus is not necessarily a fatal lesion in itself.

Case 2.—N. D. was a female child, 10 months old at the time of death. She was born at full term after a labour of eight hours' duration, the first of twins. The patient appeared mentally brighter than her twin brother. At the age of one month both developed diarrhœa and were admitted to the Boston City Hospital. Examination showed poor muscular tone, emaciation and dehydration. Vomiting of projectile type occurred several times a day. Diarrhœa was persistent. No convulsions or other neurological manifestations were noted. Lumbar puncture was not performed. The temperature was 103° F., but gradually fell to normal after two weeks. From this time forth the infant failed to develop mentally. At the time of discharge from the hospital at 4 months of age, her weight was 5 lb. She played only with her hands and her attention could not be attracted by toys. She was nervous and irritable. There were no paralyses and sensation seemed normal. At 6 months of age the infant had her first convulsion. This was generalized and lasted about ten minutes. The patient had five similar convulsions during the next two weeks.

She was admitted to this hospital at the age of 7 months. The weight was 8 lb. 8 oz. The circumference of the head was 17½ in., of the chest 13¼ in. and of the abdomen 13 in. Examination showed an underdeveloped and poorly nourished infant. There were numerous dilated blood-vessels in the scalp. The cranium was strikingly enlarged. The anterior fontanelle measured 4 by 3 cm.; the posterior fontanelle was closed. In the optic fundi there was an excessive number of vessels, the veins were tortuous and engorged, there were scattered hæmorrhages, and the optic discs presented marked papillœdema. Examination of the heart, lungs, and abdomen revealed no abnormalities. There was no spina bifida. The corneal reflexes were active. The biceps reflexes were normal, but other tendon reflexes could not be obtained. The hæmoglobin was 65 per cent., the red blood-cells 2,750,000 per c.mm. with normal white blood-cell and differential counts. On admission fluid obtained by lumbar puncture was clear; it contained a faint trace of globulin and normal sugar content. Microscopical examination revealed 620 cells, 12 of which were white blood-cells, the remainder red blood-cells. Puncture of the subdural (or the subarachnoid) space on both sides yielded grossly bloody fluid with strongly positive globulin reaction and normal sugar. Microscopical examination showed 4,800 cells per c.mm., most of which were red blood-cells. The ventricular fluid was bloody. The globulin reaction was strongly positive, the sugar content normal. There was no xanthochromia after centrifuging.

Cultures of all the fluids were negative. Roentgenograms of the skull showed wide separation of sutures. The patient was considered to have bilateral intracranial hæmatomata. These were tapped alternately every one or two days, each being drained four times. The fluid contained 179,000 to 455,000 cells per c.mm., mostly red blood-cells with white blood-cells in the usual proportions found in the circulating blood. After centrifuging the fluid was deeply xanthochromic. Cultures in all instances yielded no growth. After injection of air following tap of the right intracranial hæmatoma, roentgenograms showed a large accumulation of air over the surface of the right cerebral hemisphere which was evidently considerably collapsed. There was no air in the ventricles. Re-examination following injection of air in the left intracranial hæmatoma showed a large amount of air over the cortex, which was collapsed to the same extent as that seen previously on the right. After five weeks the patient was discharged in an improved condition.

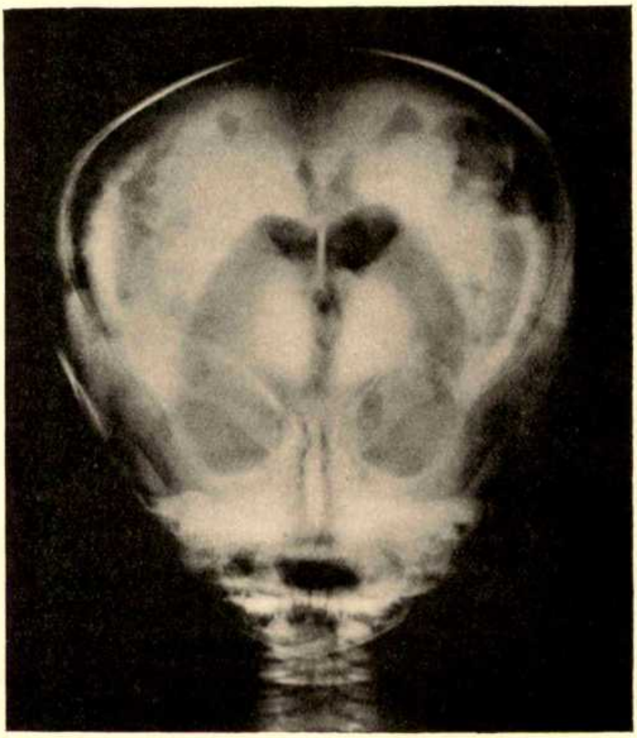

FIG. 1.—*Case* 2. Ventriculo-encephalograms showing dilatation of the lateral ventricles. There is a large amount of air over the cerebral cortex.

She did well at home for three weeks. Then one evening she vomited several times, and her mother noted that the anterior fontanelle which had been flat was bulging. She had a tonic convulsion lasting ten minutes. The patient was brought again to the hospital. Examination showed an underdeveloped and malnourished child with slow, quiet respirations. The anterior fontanelle measured 4 by 3 cm. and was very tense. There were prominent scalp veins. The pupils were equal, regular, and reacted normally to light. On ophthalmoscopic examination the fundus of the right eye showed venous congestion and slight papillœdema. The left fundus was normal. Examination of the heart, lungs and abdomen revealed nothing unusual. The biceps reflexes and the knee-jerks were equal and slightly overactive. There was no ankle clonus. The Kernig and Brudzinski signs were not elicited. There was no rigidity of the neck. Intracranial taps on each side yielded 75,000 to 100,000 red blood-cells per c.mm. with white blood-cells in proportions found in the circulating blood. The intracranial tap was repeated on the right side after two days. The increased intracranial pressure subsided and the child did fairly well for four weeks. A series of studies were then done to determine the advisability of surgical removal of the hæmatomas. Ventriculo-encephalograms showed marked dilatation of both the lateral and of the third ventricles (fig. 1). The right lateral ventricle was somewhat larger than the left. There was much air in the subarachnoid space over the cortex on both sides. The patient responded to persons and reached for coloured tubes with each hand, but did not react to tiny objects. Play with larger objects was confined to simple grasping. The child was estimated to be five to six months in mental age. The head had increased one-half inch in circumference in a month. Exploratory operation was performed five weeks after her second admission to the hospital. A large membrane was found covering the right parietal cortex. This was removed. The patient died of shock on the operating table.

Surgical specimen.—This consisted of a portion of pale pink membrane measuring 5·5 by 4·5 cm. Histologically it was made up of proliferating fibroblasts rather widely separated from one another. There were numerous dilated capillaries among the fibroblasts. Hæmosiderin-containing phagocytes were found from place to place.

Post-mortem findings.—A culture of the blood from the heart gave no growth. Abnormal findings were confined to the brain and dural sinuses. The brain weighed 735 grm. (normal weight of the brain at this age is 750 grm.) [3]. A membrane was found over the left parietal cortex which was pinkish-grey in colour and applied closely to the dura. It contained xanthochromic fluid. As the brain was removed the membrane was found to cover not only the superior surface of the hemisphere, but to ensheath almost the whole brain except in the posterior fossa and in the right parietal region where it had been removed surgically. The leptomeninges were thickened and contained numerous tortuous vessels, most conspicuous over the left parietal lobe. There was a normal amount of xanthochromic cerebrospinal fluid. The brain was symmetrical and normal in consistency. There were no recent hæmorrhages over its surface. Examination of the venous sinuses of the dura showed them all normal except the superior longitudinal sinus. In the middle third of this sinus there was a firm, greyish-white, fibrous thrombus which occupied the entire lumen. The middle ears and mastoid cells were free from exudate. A portion of the spinal cord removed from the thoracic region was normal. After fixation in formalin the brain was cut in coronal sections at 10 mm. intervals. The grey and white matter were demarcated clearly from each other. The gyri of each parietal lobe were rather small and appeared slightly shrunken, though without striking distortions. There was moderate dilatation of both lateral ventricles.

Microscopical examination.—The superior longitudinal sinus contained an organized and canalized thrombus which completely occluded the sinus at some points, while in others there was an endothelial-lined space approximately one-tenth the size of the lumen of a normal sinus. This represented either a very large canalizing space, or more probably a persistence of the original lumen. The thrombus was composed of strands of collagen arranged in roughly parallel bands, between which were a moderate number of connective tissue cells of adult type. Among these fibres were numerous large capillaries of irregular contour which were lined by a single row of flattened endothelial cells. A few mononuclear cells and lymphocytes were seen in the thrombus. Here also numerous phagocytic cells were found filled with hæmosiderin granules.

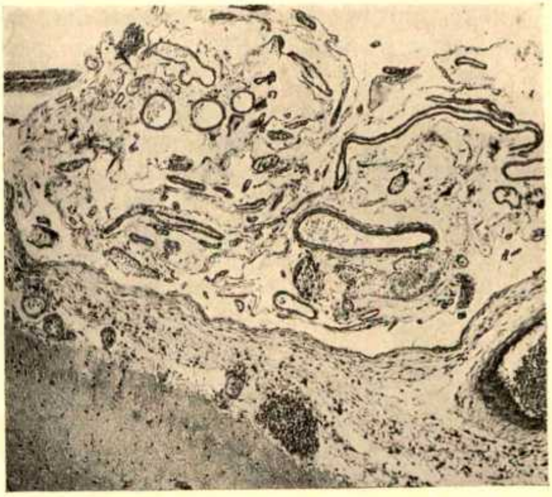

FIG. 2.—*Case* 2. An irregular plexus of newly formed vessels over the arachnoid of the right parietal cortex. Hæmatoxylin and eosin, × 75.

There was an increased number of veins in the leptomeninges, some of which could be followed for long distances into sulci along with the pia mater. All of the vessels were distended with red blood-cells. No fibrinous or organized thrombi were found in any of these vessels. In a section of the left parietal cortex, a complex cluster of vascular channels was found over the surface of the arachnoid (fig. 2). Most of the vessels presented narrow layers of smooth muscle about their flattened endothelium. None contained elastic tissue. Among these larger vessels were smaller ones with a single layer of endothelium surrounded by a connective tissue basement membrane. Between the vascular channels delicate strands of connective tissue were found. Sections of various portions of the brain showed no areas of necrosis, softening or gliosis.

Comment.—A patient with such a history and clinical course is usually considered as an example of certain sequelæ of birth trauma, but this particular case merits further analysis. It is clear that this patient was in better physical and mental condition than her twin brother at 1 month of age, though neither had gained much weight. Then the patient and her twin brother had acute nutritional disturbances. The brother recovered and developed normally thereafter. The patient recovered from the acute illness which lasted for two weeks, but from this time on she was greatly retarded in her mental as well as in her physical development. There were no convulsions or other prominent neurological manifestations until the patient was 6 months of age. At 7 months of age she had an enlarged cranium, evidence of increased intracranial pressure, and dilated scalp and retinal vessels. Cerebrospinal fluid from various sources contained blood. She failed to respond to treatment and died after operation for removal of an intracranial hæmatoma.

The important pathological findings were an organized thrombus which occluded the middle one-third of the superior longitudinal sinus, an increased vascularity of the leptomeninges and hæmorrhages into the leptomeninges and the subdural space.

As in the previous instance (Case 1), we can establish no absolute interdependence of the organized thrombus in the superior longitudinal sinus and the intracranial hæmorrhages. That birth injury was the cause of the hæmorrhages seems improbable. Other causes of intracranial hæmorrhage, except thrombosis of the superior longitudinal sinus, can be dismissed as very improbable in this particular instance. We believe from our studies of acute sinus thrombosis [1, 2] that the hæmorrhages were secondary to thrombosis of the superior longitudinal sinus. The probable sequence was : The patient had a period of normal postnatal development, but during the course of an acute nutritional disturbance a thrombus formed in the middle one-third of the superior longitudinal sinus. The patient survived the acute illness but the thrombus partially obstructed the middle superior cerebral veins. As a result of the venous obstruction there was hæmorrhage into the meninges and the subdural space. Symptoms of retardation of mental development immediately followed recovery from the acute nutritional disturbance. The subdural hæmatomas gradually enlarged in the manner described by Zollinger and Gross [4]. At six months of age, five months after the onset of the acute illness and appearance of symptoms of mental retardation, convulsions developed. There is nothing in the clinical history or the pathological findings which is not in conformity with this interpretation.

Case 3.—The patient, R. D., was a white male infant, 3½ months of age at the time of death. He was the first child of young, healthy parents. Birth occurred in another hospital at full term. Delivery was spontaneous after a labour of twelve hours' duration. The birth weight was 7 lb. 4 oz. The child appeared normal in every way at the time of birth. He was followed closely by the family physician, who considered the patient to be developing entirely normally until 4 weeks of age, when for a few days he had diarrhœa, the stools containing mucus but no blood. Then at 7 o'clock one morning the patient was noted to become flaccid suddenly, as if dead, and shortly afterwards had a convulsion lasting twenty minutes. This was characterized by tremor of the hands and legs with hyperextension of the back and head. There were three similar seizures within a few hours. The temperature was 105° F. The patient was sent to another hospital. The entire body was cyanotic and the lower extremities were held rigidly. There was a tremor of the hands. Neck rigidity was not present. The pupils were equal. Another convulsion occurred soon after arrival at the hospital, but during the next week no further seizures occurred. The diarrhœa persisted and the temperature ranged between 103° F and 105° F. The baby's legs were held rigidly. Lumbar puncture was not performed. The infant's condition gradually improved and he was sent home afebrile after a week's stay.

Shortly after return home he had one to three short seizures a day, each consisting of flexion of the thighs on the abdomen and holding the breath with resultant cyanosis. The patient became extremely restless and slept very little. He was aroused by slight stimuli and cried a great deal. Despite this the patient regained most of the weight lost during his acute illness. Because of the continued convulsions and irritability, the patient was brought to this hospital at 2 months of age. At that time the height was 24 in., the head 16½ in. in circumference, the chest 17 in., the abdomen 14½ in. He was well developed and nourished. There was marked hypertonia and the patient often seemed startled without any definite external stimulus. He resisted all attempts to extend the arms and legs, which were held so rigidly as to permit support of his own weight. There was spontaneous nystagmus. Questionable tâche cérèbrale was observed. The anterior fontanelle measured 4 × 4·5 cm.; the posterior 0·2 × 0·2 cm. Neither was bulging. The pupils were equal and regular and reacted normally to light. The chest, abdomen and genitalia revealed no abnormalities. The knee-jerks, ankle-jerks and triceps and biceps reflexes were over active. The rigidity of the legs interfered with testing for Kernig's sign; there was no stiffness of the neck. Agglutination tests on the blood for enteric organisms were negative. The spinal fluid at first was clear, but after a few c.c. had been withdrawn it became distinctly xanthochromic. The first portion contained 83 red blood-cells, the second 380 red blood-cells per c.mm. Three subsequent lumbar punctures revealed similar findings. Encephalograms showed dilated, rounded, symmetrical ventricles with a large amount of air over the cortex of both hemispheres, and loss of convolutional markings (fig. 3). The patient was discharged after seventeen days unimproved.

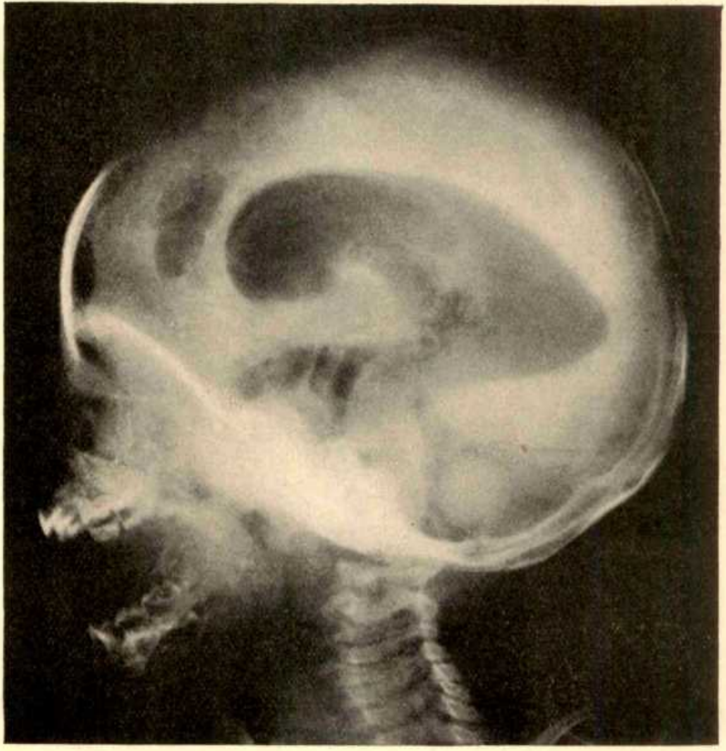

FIG. 3.—*Case* 3. Ventriculo-encephalograms, showing dilated lateral ventricles.

Ten days later he was readmitted to hospital. During the first portion of the interval the infant did fairly well, but had occasional twitchings from time to time. Three days before entry he began to vomit after each feeding and had frequent green watery stools, increasing to ten on the day before admission. On entry the anterior fontanelle was greatly sunken, the temperature was 100° F. and the patient was pale and irritable. As on the previous admission there was generalized muscular hypertonicity. The pupils were normal. The optic discs showed physiological cupping. There was right otitis media. The course was progressively downhill. Death occurred at $3\frac{1}{2}$ months of age, eleven days after readmission to the hospital and two and a half months after the onset of the acute illness.

Post-mortem findings.—The brain weighed 208 grm. (normal weight at this age 528 grm.) [3]. When the calvarium was removed about 75 c.c. of xanthochromic fluid escaped. The falx and tentorium were intact. There were numerous tenuous fibrous adhesions between the dura and arachnoid. In some areas there were pockets of xanthrochromic fluid among these intermeningeal adhesions. The arachnoid was opaque in many areas and greyish brown in colour throughout. The brain was roughly symmetrical and moderately firm in consistency. The convolutions of the cerebral hemispheres adjacent to the falx were more shrunken than elsewhere. Over most of the convexity of the brain the convolutions were small and irregular in outline, but their general pattern was normal in miniature (fig. 4). The convolutions at the base of the brain were normal in arrangement and size (fig. 5). The shrunken appearance

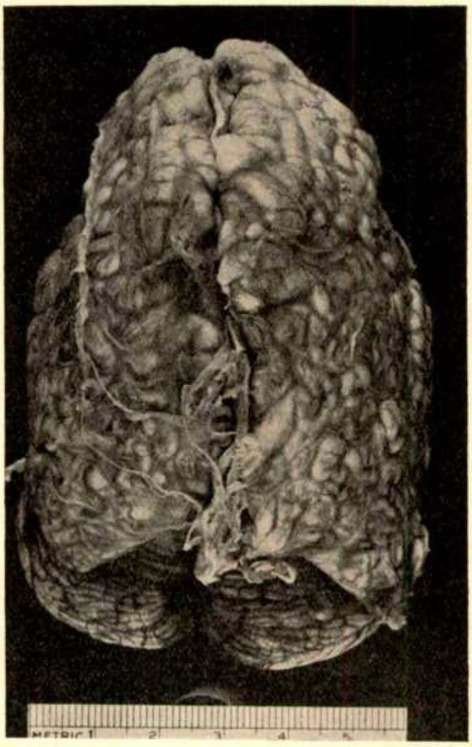

FIG. 4.—*Case* 3. Superior surface of the brain. Note the numerous cord-like cerebral veins, some of which contain organized thrombi. The convolutions are shrunken but conform in general to the normal pattern.

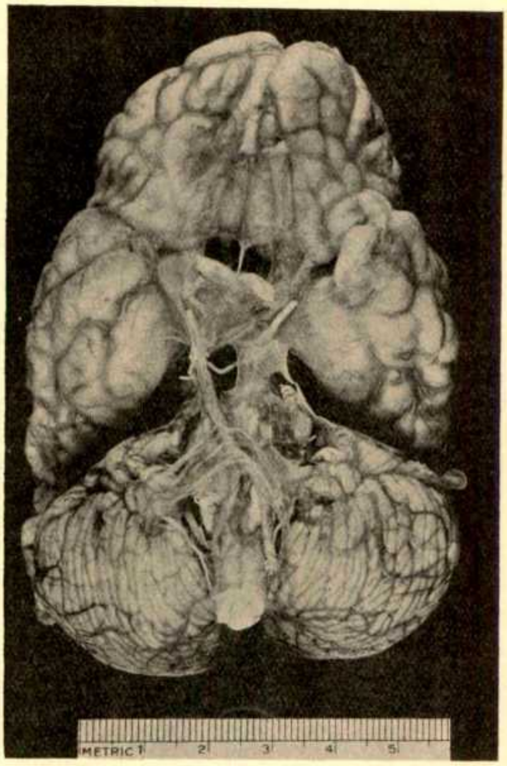

FIG. 5.—*Case* 3. Inferior surface of the brain. Note the well-developed basilar convolutions and the normal architecture of the cerebellum and brain-stem.

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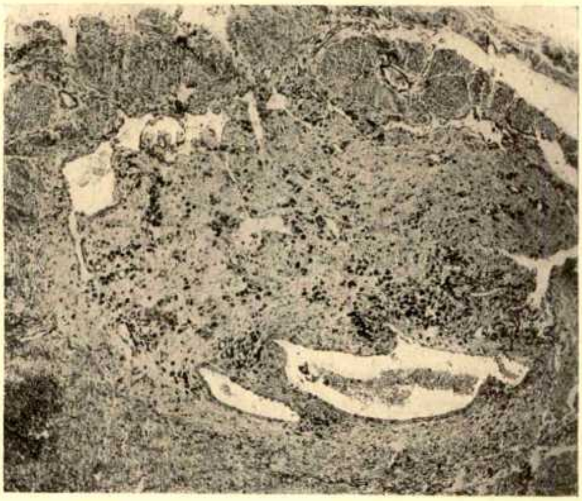

FIG. 6.—*Case* 3. The superior longitudinal sinus is occluded by an organized and canalized thrombus. The coarse fibres of the sinus wall are seen about the thrombus. The dark areas are phagocytes containing large amounts of hæmosiderin. Hæmatoxylin and eosin, × 75.

of the convolutions was most marked in the occipital and parietal lobes. The most anterior convolutions of the frontal lobe escaped entirely and the contour and consistence of the pons, medulla and cerebellum was unaltered. The arteries of the basilar region and of the circle of Willis were normal in arrangement, and contained no thrombi or emboli. The superior longitudinal sinus was completely occluded in its anterior half by a firm, white thrombus, and no lumen could be demonstrated in this portion (fig. 6). All other dural sinuses were normal and contained fluid blood and post-mortem clots. There was a small amount of yellow exudate in each middle ear from which *Staphylococcus aureus* was cultured.

After fixation in formalin the total length of each cerebral hemisphere was 10·5 cm., the greatest height 7·5 cm., and the greatest width 2·5 cm. The occipital lobes measured 3 cm. in antero-posterior diameter. Many gyri over the convexity of each cerebral hemisphere were small and shrunken, but normal in arrangement. Along the shallow sulci there were numerous large blood-vessels. The parietal lobe occupied about 4 cm. of the length of the brain and averaged 4 cm. in height. The precentral and postcentral gyri averaged 0·5 cm. in width. The central sulcus was very shallow. The other parietal gyri were shrunken to a somewhat less extent. Over this region there were numerous wide vessels, close together, running along the shallow sulci. The frontal lobes each were 4·5 cm. in greatest antero-posterior diameter. Their gyri were somewhat irregular in outline, but in the most anterior portion of the lobes were developed normally. The meningeal vessels were less numerous here. The gyri at the base of the brain were approximately normal in size and arrangement. The supracallosal gyrus was shrunken and covered by numerous prominent vessels. The hippocampus was not unusual.

On section the grey matter was distinct from the white in some areas, but the distortion of gyri in most places was extreme. In some gyri there was a band of grey matter under the pia ; in others there were numerous honeycombed areas often occupying almost an entire gyrus. These cystic zones were usually separated from the pia by a narrow line of grey matter (fig. 7). These areas were numerous in the gyri of the convex and medial surfaces of each cerebral hemisphere, but were not found in those of the inferior surface. One was present in the island of Reil. They varied from 0·2 to 0·5 cm. in diameter. Beneath these there were greyish irregular zones in the white matter distorting the usual markings of the fibre tracts. The lateral ventricles were moderately dilated, the right being slightly smaller than the left. The caudate nuclei were well formed. The thalami were shrunken, but presented the usual landmarks. The 3rd ventricle measured 1 cm. in breadth and 1·5 cm. in supero-inferior diameter. The ependyma was glistening and free from exudate and hæmorrhage, though occasionally it had a pitted appearance. Beneath it numerous prominent blood-vessels were visible. There was no evidence of occlusion of the ventricular system. The aqueduct and 4th ventricle were not dilated and their ependymal surfaces were normal. The pons and medulla presented their usual markings. The cerebellar folia were well developed and free from distortion, hæmorrhage and softening.

Microscopical examination.—Sections from the superior longitudinal sinus showed it to be entirely occluded throughout the anterior one-half of its course by an organized and canalized thrombus (fig. 6). The thrombus was made up of loosely arranged collagen fibres among which were fibroblasts of adult type. Among the collagen fibres were many phagocytic cells filled with hæmosiderin and numerous small vascular channels lined by a single layer of endothelium. None presented smooth muscle in their walls. While most of the channels were small, two of them were considerably larger than the others. Since neither of these was adjacent to the sinus wall they were interpreted as large, newly formed vessels rather than as the persistent original lumen of the sinus. There was no evidence of inflammatory reaction or of recent thrombosis. The dura adjacent to the sinus wall contained scattered phagocytes filled with hæmosiderin.

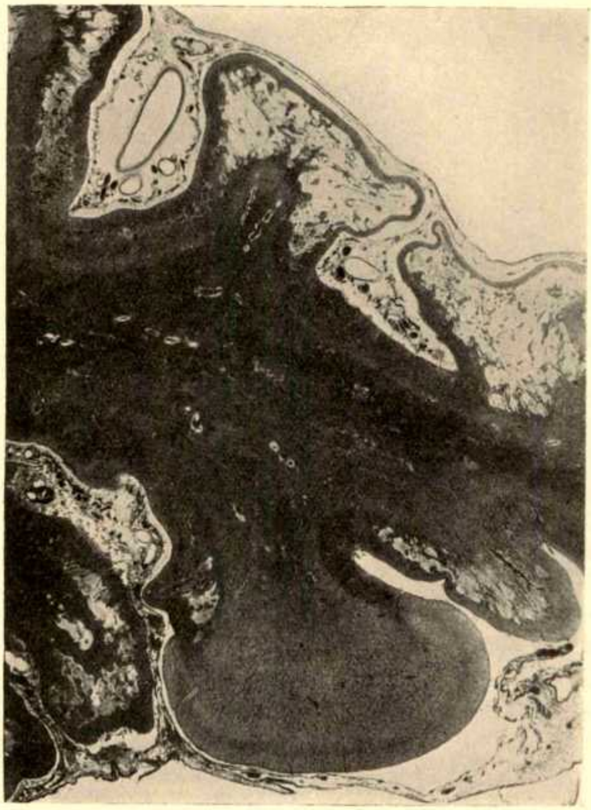

FIG. 7.—*Case* 3. Low power photomicrograph of several parietal gyri. The block has been chosen to give true cross sections of the gyri. There is a convolution which is normal in general shape at the bottom. It contains only a small lesion. The other convolutions show various degrees of destruction with partial repair. Note the increase in vascularity of the leptomeninges. Weigert's method for myelin sheaths, × 11.

The leptomeninges in all portions presented an increase of the connective tissue, and occasional lymphocytes and mononuclear cells, and phagocytic cells filled with hæmosiderin were found in the regions of fibrosis. The blood vessels were increased in number and in size. The newly formed vessels were in some instances large with smooth muscle in their walls, but were more often composed of a single layer of endothelium backed up by connective tissue. These large, dilated vessels were found in all portions of the pia-arachnoid over the convexities of the cerebral hemispheres, but were especially prominent in the sulci. In a few places organized and canalized thrombi were demonstrable microscopically in the superior cerebral veins even at some distance from the superior longitudinal sinus. These resembled in general structure the thrombus in the dural sinus already described. There were no fibrinous thrombi. The vascularity of the meninges over the cerebellum was very little altered from the normal.

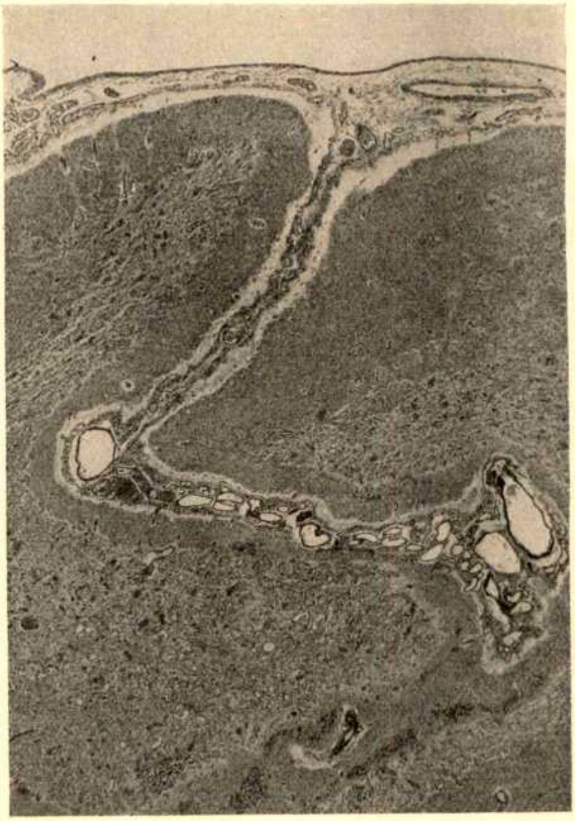

FIG. 8.—*Case* 3. There is a marked increase in vascularity of the meninges. The normal cerebral tissue is lacking and there is evidence of repair. The black dots in the grey matter near the bottom of the illustration are small areas of calcification. Hæmatoxylin and eosin, × 32.

The cerebral cortex presented various pictures in different parts (fig. 7). In some regions, normal gyri could be found with the architectural layers intact and the nerve cells free from degeneration. In others, there were changes of varying extent. At times, connections between the lesions and the subarachnoid space could be identified. The lesions usually involved the third to the sixth layers of the cerebral cortex, but the alterations extended of some degree into the white matter. The lesions consisted in necrosis of normal tissue and a late stage in its repair. The cystic spaces seen by the naked eye corresponded to areas where normal tissue elements were lacking, but in which the zone was occupied by compound granular corpuscles filled with vacuoles containing material staining faint blue with Weigert's method for myelin. There were a few newly formed blood-vessels in these regions. In the areas where such lesions communicated with the subarachnoid space, newly formed blood-vessels were very numerous and were accompanied by collagen fibres.

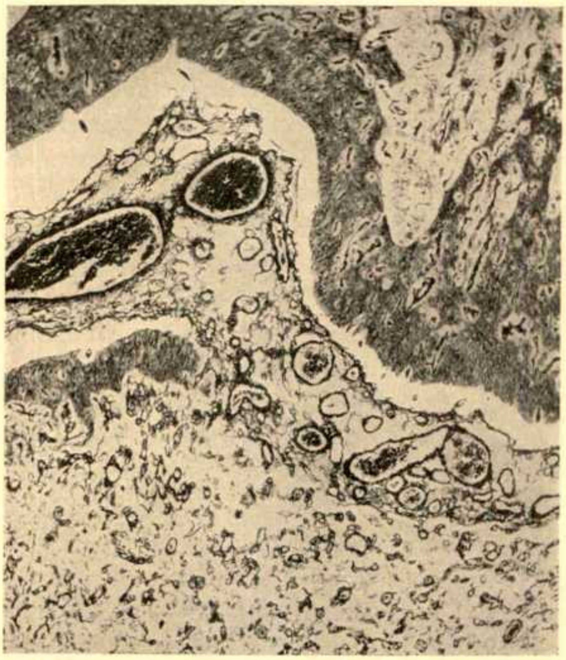

FIG. 9.—*Case* 3. Organization of an area of necrosis by blood-vessels, in part derived from the leptomeninges, which are much increased in vascularity. Laidlaw's method for connective tissue, × 75.

In other areas normal tissue elements were lacking, and were replaced by astrocytes with compound granular corpuscles among their processes. Still farther out there were areas made up wholly of astrocytes, which gradually diminished towards zones of normal cerebral tissue. In places these lesions occupied an entire gyrus, which then appeared shrunken, in other places only part of a gyrus was involved, and certain gyri escaped entirely. Weigert's myelin sheath stain showed the white matter to be fairly well myelinated for a patient aged 3½ months. In the normal gyri there was the usual arrangement of myelinated fibres, while in the degenerated gyri myelin sheaths were not seen. The basal ganglia were poorly defined owing to a large amount of astrocytic proliferation. The subependymal glia was increased in amount. There were no changes in the ependymal cells themselves. Sections of the pons and medulla showed nothing unusual. There were no areas of degeneration in the cerebellum, but two or three rows of cells were found beneath the pia as remnants of the external granular layer. The fibrillary and internal granular layers were well developed. The Purkinje cells were free from degeneration. The fibre tracts of the spinal cord were normally myelinated.

Comment.—There were certain pertinent details in the history of this patient. The infant developed normally during the first month of his life. Then during the course of an acute nutritional disturbance, characterized chiefly by a diarrhœa, there was a sudden onset of severe convulsive seizures. Although the patient recovered from the acute illness, the convulsions persisted. Within a short time other nervous manifestations such as irritability, hypertonicity of the extremities and over active tendon reflexes became prominent. An examination of the spinal fluid at two months of age disclosed xanthochromia and a number of red blood-cells. Encephalograms showed dilated ventricles, abnormal contour of convolutions and an excessive amount of air over the cortex of each cerebral hemisphere. There was no improvement of the condition of the patient from the neurological viewpoint. He died two and a half months after the onset of nervous manifestations.

At necropsy, there was a small brain with normal basal convolutions, but distorted atrophic convolutions over the convexity of each cerebral hemisphere. The abnormal convolutions for the most part were restricted to the region drained by the middle superior cerebral veins. The cortical and subcortical lesions consisted largely of foci of necrosis with evidences of repair. The pia-arachnoid was thickened and unusually vascular. There was evidence of old hæmorrhage into the pia-arachnoid and subdural space.

The anterior one-half of the superior longitudinal sinus was occluded by a firm, fibrous vascularized thrombus. This was so localized as to obstruct almost completely the venous drainage from the regions of the brain affected by the degenerative changes. It is of particular significance that organized and canalized thrombi were demonstrated in the superior cerebral veins.

In this patient, we have no hesitancy in reconstructing the sequence of events as follows: There was normal development of the brain to one month of age. During an acute nutritional disturbance, a thrombus formed in the superior longitudinal sinus with extension into tributary cerebral veins. Bilateral cortical and subcortical necroses with attendant hæmorrhage, especially into the pia-arachnoid, were the consequences. The infant recovered and the thrombi organized, but the damage had been done. Unaffected portions of the brain, especially the basal convolutions, developed normally.

Discussion.

The three patients whose clinical and pathological states have been presented exhibited organized and canalized thrombi in the superior longitudinal sinus. They furnish adequate demonstration that thrombosis of the superior longitudinal sinus does not invariably result fatally in a few days.

It is possible that in the first patient a cerebral infarct may have resulted from an embolus, or that it may have been due to partial occlusion of the dural sinuses. Case 2 presented intracranial hæmatomata, new vessel formation and hæmosiderin deposits in the leptomeninges. These are the results of intrameningeal and subdural hæmorrhage at the time of the acute thrombosis. Case 3 shows very clearly the end-result of venous obstruction, subarachnoid hæmorrhages and cerebral necroses.

The thrombus in the first patient was probably infectious in origin, resulting from the otitis media from which he was suffering at that time. Each of the other two patients developed normally to up the time of an acute illness, characterized by nutritional disturbance of considerable severity, pyrexia, dehydration and, in Case 3, abnormal neurological findings. These are the clinical manifestations most frequently seen in patients with sinus thrombosis unassociated with sepsis or surgical procedures. In each patient there was retrogression in mental development as well as abnormal neurological manifestations. Death occurred after several months as a result of intercurrent developments. These patients, then represent instances of acquired cerebral lesions in childhood.

Every neurologist is repeatedly faced with the problem of explaining the onset of nervous symptoms without any apparent cause in infants and young children who have had a period of normal development. These symptoms and signs of disturbance of the central nervous system often follow some severe acute illness. In other instances no direct relationship is apparent. In certain of these patients the pathologist is confronted with the presence of structural alterations in the brain which are essentially degenerative or reparative, local or extensive. We believe from evidence presented in previous articles [1] [2] that the sequelæ of thrombosis of the dural sinuses must be considered seriously in the analysis of these clinical and pathological abnormalities.

The origin of such lesions are readily obscured by various factors. In the first place the acute illness, even though accompanied by disturbances of muscle tonus or even convulsions, varies but little from the severe nutritional disturbances frequently encountered in infants under 2 years of age. None the less, such clinical manifestations are all that are seen in many patients who die with thrombosis of the superior longitudinal sinus in the acute stage. In patients who later develop neurological abnormalities the acute illness is often interpreted in retrospect as "encephalitis." The symptoms may be progressive, and for that reason the significance of the initial illness is set aside.

The anatomical nature and distribution of the lesions in acute sinus thrombosis have been discussed previously. It should be recalled that the lesions in the meninges are hæmorrhage and venous obstruction, often accompanied by thrombosis of cerebral veins. Within the brain substance, there are areas of softening, often associated with hæmorrhage.

If it is assumed that recovery from such lesions can occur necropsy at a later period should show pathological changes. Subdural and intradural hæmorrhages, if small, would leave areas of hæmosiderosis; if large, they may become encapsulated. Evidence of repair in the leptomeninges should include hæmosiderin granules in phagocytes and some increase in connective tissue as a reaction to the extravasation of blood. These were present in all three cases. The venous obstruction would result in dilatation of previously existing vessels and, after an interval, formation of new vascular channels. These were also encountered in each of the three instances. Of special interest is the small plexus of veins over the surface of the arachnoid in Case 2 (fig. 2).

The results of the intracerebral necroses and hæmorrhages are of first importance to the present discussion. In Case 3 large areas were found in which almost the only cells were compound granular corpuscles filled with droplets of degenerating myelin; normal cerebral structure was entirely lacking. At the periphery of these lesions there was extensive astrocytosis. In the intervening regions astrocytes, collagen fibres and newly formed blood-vessels and compound granular corpuscles were intermingled. There is a striking resemblance of such tissue to those traumatic scars which pull on the entire vaso-astral framework of the brain producing Jacksonian epileptic attacks [5]. In the brain studied, however, the changes were less advanced than those in the usual case of traumatic epilepsy. Such scars might be expected if the patient had lived for a longer period, and glial cysts and focal areas of gliosis might be found.

In conclusion, it should be mentioned that it is easy to overlook small thrombi in the superior longitudinal sinus at necropsy, especially if they are organized. We urge that careful histological studies be made of this structure in patients with acquired cerebral defects.

SUMMARY.

The present report is concerned with a clinical and pathological study of three children who presented organized and canalized thrombi in the superior longitudinal sinus. These were found in a series of eighty instances of sinus thrombosis of all types, the seventy-seven instances with more recent thrombi having been discussed elsewhere [1].

One patient developed acute neurological disturbances in the course of cardiac decompensation resulting from mitral stenosis of rheumatic origin. At necropsy organized and canalized thrombi were found in the superior longitudinal and right lateral sinuses. There was a zone of organizing hæmorrhage and softening in the cerebral cortex.

The other two patients were infants who developed normally up to the time of acute illnesses, characterized by severe diarrhœa and vomiting. As pointed out previously, these were prominent symptoms in those patients who died with acute sinus thrombosis unassociated with surgery or demonstrable sepsis. During the illness of one patient and shortly after the subsidence of acute symptoms in the other patient, it became obvious that there was impairment of mental function. Death occurred several months later. Portions of the superior longitudinal sinus of each patient contained organized and canalized thrombi. The pathological changes in the brain and meninges, allowing for such repair as might be expected after a few months, conformed with those changes which are commonly associated with thrombosis of the superior longitudinal sinus of short duration.

We believe that the patients here reported give support to our contention that certain acquired cerebral defects are due to thrombosis of the superior longitudinal sinus and its sequelæ. The possible relation of cerebral lesions secondary to sinus thrombosis and non-traumatic scars

of the cerebrum associated with Jacksonian epilepsy is emphasized. The organized thrombi may be small and easily overlooked, as unless the entire lumen is occluded the process of organization tends to greatly reduce their size. A thorough search of the dural venous sinuses for the presence of organized thrombi may elucidate the ætiology of some instances of focal cerebral gliosis, "encephalitis," of childhood and spontaneous subdural or subarachnoid hæmorrhage.

BIBLIOGRAPHY.

[1] BAILEY, O., and HASS, G. "Dural Sinus Thrombosis in Early Life. I. The Clinical Manifestations and Extent of Brain Injury in Acute Sinus Thrombosis," *Journ. Ped.* (in press).

[2] BYERS, R., and HASS, G. "Thrombosis of the Dural Venous Sinuses in Infancy and in Childhood," *Amer. Journ. Dis. Child.*, 1933, **45**, 1161.

[3] COPPOLETTA, J., and WOLBACH, S. "Body Length and Organ Weights of Infants and Children. A Study of the Body Length and Normal Weights of the More Important Vital Organs of the Body between Birth and Twelve Years of Age," *Amer. Journ. Path.*, 1933, **9**, 55.

[4] ZOLLINGER, R., and GROSS, R. "Traumatic Subdural Hæmatoma. An Explanation of the Late Onset of Pressure Symptoms," *Journ. Amer. Med. Assoc.*, 1934, **103**, 245.

[5] (*a*) FOERSTER, O , and PENFIELD, W. "The Structural Basis of Traumatic Epilepsy and Results of Radical Operation," *Brain*, 1930, **53**, 99. (*b*) PENFIELD, W. "The Mechanism of Cicatricial Contraction in the Brain," *Brain*, 1927, **50**, 489.

ABNORMALITIES IN THE AMOUNT AND CIRCULATION OF THE CEREBROSPINAL FLUID ASSOCIATED WITH OTITIS MEDIA.

BY ADAMS A. McCONNELL.

THE search for an otogenous intracranial abscess not uncommonly reveals, instead of an abscess, an excessive amount of normal cerebrospinal fluid under increased pressure (Symonds [1]). If a temporal approach has been made this fluid may be found in the descending horn of the lateral ventricle; if the posterior cranial fossa has been opened the fluid may be discovered in the subarachnoid space behind the petrous temporal bone. Either finding is compatible with the presence of a communicating or external hydrocephalus, but the first is more suggestive of an obstructive internal hydrocephalus, and the second of a localized cystic collection of fluid in the posterior fossa (encysted arachnoiditis). The interpretation of what is found at operation is therefore not always easy.

This paper deals with the operative findings in six cases of otitis media. These cases presented symptoms so suggestive of intracranial complications that exploratory operations were performed. In all the cerebrospinal fluid was normal, and in none was an abscess present.

Case 1.—Female, aged 33. Simple left mastoid operation. Lateral sinus thrombosis. Headache. Papillœdema. Nystagmus. Negative exploration of left temporal lobe. Exploration of the posterior fossa; excess of cerebrospinal fluid in front of the left lobe of the cerebellum. Complete recovery.

Mrs. A. E., aged 33. Admitted on May 4, 1935, to the Richmond Hospital, Dublin, under the care of Mr. Stafford Johnson, with the diagnosis of acute infection of the left mastoid. Four weeks before admission both maxillary antra had been drained, and for ten days she had suffered from headache and earache. On admission temperature was 101·8° F., pulse 120 and respirations 22.

May 4: An emergency mastoid operation was performed. Pus was found in the bone down to the lateral sinus which was exposed and which appeared healthy.

May 6: The temperature reached normal and the pulse rate was 88.

May 7: She had a rigor and a temperature of 101·8° F. A diagnosis of lateral sinus thrombosis was made. The left internal jugular vein was ligatured in the neck; the lateral sinus was exposed, opened and a clot removed.

May 8: Temperature normal in the evening. Pulse 84. Felt well.

May 9: Rigor. Temperature 100° F. Pulse 100.

May 10: Temperature normal. Pulse 96. Felt well. Good appetite.

May 13: Got up for a short time.

May 15: Temperature rose to 101·5° F. Pulse 92.

During the next week there were fluctuations of temperature up to 101° F., but no cause could be discovered. The patient felt sick and complained of pain in the back of the head.

May 25: She complained of pain behind the eyes. Temperature 98·4° F. and pulse 98.

Next day pain behind the eyes had disappeared, but was present in the occipital region.

May 27: Pain in the back of the head. Temperature 102° F. She said that her left arm felt weak.

General neurological examination was negative.

Ophthalmological examination by Mr. Alan Mooney revealed a right choked disc of 3½D, numerous exudates on disc and few small hæmorrhages. Retinal veins very congested and tortuous. The left disc was swollen to 2D; appearance suggest sudden onset. Veins less congested and tortuous than on right side. Slight limitation of right lateral gaze. Nystagmus on lateral gaze, the movements slower and coarser on looking to right. Nystagmus also present on upward deviation.

May 29: Temperature reached 101·5° F. but next day it was normal.

After this date the patient had no headache and felt well in every way. The papillœdema, however, did not subside.

June 8: Temperature rose to 99·2° F. No subjective symptoms. Lumbar puncture pressure was not increased and the cerebrospinal fluid was normal. The papillœdema slowly increased and on June 20 the swelling was 4D in the right eye and 3½D in the left eye.

June 21: With the patient lying on the left side, the right ventricle was punctured. The ventricle was found in the normal position and the fluid rose only to the top of the needle. Only 7 c.c. of fluid could be obtained. It was normal.

June 24: The papillœdema was 4½D in the right eye and remained at 3½D in the left eye, and there were two fresh hæmorrhages in each retina. Nystagmus as before. Perimetric studies showed full fields with slight enlargement of the blind spot in each eye. Visual acuity in both eyes was $\frac{6}{6}$.

The steady increase in papillœdema made active measures imperative, so a needle was passed into the right ventricle in the hope of obtaining a ventriculogram, but as only 3 c.c. of fluid were obtained, there was too little air to obtain a picture.

As there was no internal hydrocephalus it was decided to explore the left temporal lobe. This was done under general anæsthesia with negative results.

An opening was then made over the left lobe of the cerebellum. There was no gross increase of tension. A needle was passed into the middle of the lobe and directed towards the base of the petrous part of the temporal bone. At a depth of 6 cm. from the surface of the cerebellum a slight obstruction was encountered. This was overcome without force and some fluid appeared. It flowed gently and was not under marked tension. With a syringe 2 oz. of this fluid were aspirated slowly. Towards the end it became bloodstained. Free pulsation now appeared in the cerebellar lobe. The wound was closed in the usual way without drainage.

The fluid was cerebrospinal fluid, but it contained too much blood for cell count. It was sterile on culture. The patient made an uneventful recovery and was discharged on July 7, 1935. The papillœdema subsided slowly.

The latest report from this patient, received in March, 1937, was that she had been quite well since leaving hospital.

Final Diagnosis.—Collection of cerebrospinal fluid localized in the posterior cranial fossa in front of the left lobe of the cerebellum.

Comment.—The striking feature of this case was the absence of tension both on lumbar and ventricular puncture in the presence of gross papillœdema.

Case 2.—*Female, aged* 27. *Left otitis media. Two mastoid operations. Headache and vomiting. Papillœdema absent. Exploration of posterior fossa; collection of cerebrospinal fluid found in front of the left lobe of cerebellum. Complete immediate recovery, possible late recurrence.*

S. B., aged 27, was referred by Dr. MacArdle, Castleblayney, on June 24, 1935, on account of persistent headache. In 1929 she had a discharge from the left ear. This stopped inside a few weeks. She continued well for three years, when the discharge returned. In November, 1932, she got an acute mastoid infection, for which Mr. P. J. Keogh performed a simple mastoid operation. In July, 1933, there was some local pain and renewed discharge, so a radical mastoid operation was performed. Erysipelas developed in the wound, but in the course of four weeks healing was complete except for a minute sinus from which there was an occasional discharge of thin pus.

From the date of the radical mastoid operation the patient complained of practically continuous headache, with exacerbations of extreme severity accompanied usually by vomiting. During the exacerbations she was quite unable to work, and in the intervals her work was not satisfactory.

June, 1935: General medical and neurological examinations were negative. Ophthalmological examination showed full fields and normal fundi. No nystagmus. The sinus in the mastoid wound was dry. Mr. Keogh thought that the condition of the mastoid could not account for her symptoms. As the patient thought that the headache was somewhat relieved when the sinus discharged, we made a tentative diagnosis of an extradural abscess, the tension of which was relieved by the intermittent discharge.

July 5: Under general anæsthesia a curved incision independent of the mastoid wound was made to expose the bone behind the left lateral sinus. The bone appeared quite normal on exposure, and when an opening of about 2 cm. in diameter was made the dura was normal. A curved director was passed between the dura and the bone towards the mastoid but nothing abnormal was encountered. The dura was then opened. The cerebellum was normal in appearance but did not pulsate. A needle was passed into the cerebellum in the direction of the mastoid, and at a depth of 4 cm. tapped fluid. The fluid was clear and flowed slowly from the needle. After one ounce had been collected a syringe was attached to the needle and another ounce aspirated. There was then free pulsation of the cerebellum. The wound was closed without drainage. The fluid was cerebrospinal fluid, normal in every respect. Next day the patient said that she was free from headache for the first time for two years.

Three days after the operation the temperature showed some irregularity, rising to 99° or 100° F. in the evening. There was no headache nor rigidity of the neck and the patient felt and looked well. Radiographic examination of the chest showed slight density over the lower lobe of the right lung. There were no clinical signs of pulmonary disease. The temperature settled down inside a week and the patient was discharged on July 20, 1935.

For the next six months the patient was apparently perfectly well and the sinus remained closed. In January, 1937, the headaches returned. They occurred soon after rising, got gradually worse during the day and were usually relieved when she lay down with the head low at night. During the headache the occipital wound was sometimes very tender.

She was seen in April, 1937. There was pulsation at the site of the cerebellar exposure but no tension.

The latest reports state that she still suffers from headache.

Case 3.—Female, aged 24 years. Left otitis media. Facial palsy. Headache. Vomiting. Subtentorial decompression. Recovery.

Miss M. K., aged 24, was referred to the Richmond Hospital, by Dr. Geoffrey Bewley on account of headaches. In the beginning of March, 1934, she complained of a sore throat and a few days afterwards developed otitis externa and erysipelas followed immediately by paralysis of the left facial nerve. Herpes oticus was suspected, but the appearances were much more suggestive of erysipelas. The middle ear then became inflamed and the membrana tympani was punctured. Recovery was complete except for the facial palsy which persisted. During April she began to suffer from intermittent headache accompanied for a time by vomiting. In May a complete neurological examination was made: there was complete paralysis of the left facial nerve with normal electrical reactions. Slight tremors of the hands and dysdiadochocinesia of the left hand. She was unable to stand alone and deviated to the left when walking. Lumbar puncture showed a pressure of 200 mm. water and the fluid was normal. Ventricular puncture was attempted, but the ventricle could not be found. There was no evidence of tension when the opening for the ventricular puncture was made. She was discharged to her home unrelieved. She was re-admitted on October 26, still complaining of headache. Her other symptoms were unchanged. A needle was passed into the left ventricle and 10 c.c. of fluid, which was not under tension, were removed. This procedure gave her definite relief, but fourteen days later she got into a presumably hysterical condition in which she appeared unable to speak or put out her tongue, and sensation was diminished all over the body. This lasted for nearly two days, but passed off leaving her rather better than before. She passed the next three months partly in hospital, partly at home, and the headaches gradually increased in frequency and severity. She was readmitted to the Richmond Hospital on March 16, 1935. The headaches were worse than ever and were chiefly frontal and occipital. Dr. H. L. Parker found paralysis of the left frontalis muscle with spasm of the orbicularis palpebrarum and of the muscles of the lower part of the face. The tendon reflexes were increased on the right side of the body. There was a rise in temperature each evening to 99·5° or 100° F. Blood-sugar was 160 mg. per cent. and blood urea 57 mg. per cent. General medical examination was negative. On March 23, the left ventricle was punctured. The fluid was not under tension and was completely normal. In spite of the "hysterical" attack it was considered that the persistent and incapacitating headache had an organic basis and that this might be found in the posterior fossa.

On April 11, 1935, exploration of the left side of the posterior fossa was carried out, but no abnormality was discovered. The patient was thus left with a limited subtentorial decompression. She made a prompt recovery from the operation, and from that date until the present she has had no headaches. When seen last in January, 1937, she was perfectly well except for paralysis of the left frontalis muscle and spasm of the other muscles on that side of the face.

Comment.—Lumbar and ventricular punctures did this patient no good, but cerebellar decompression has apparently cured the headaches. It may be that at operation a collection of fluid in the lateral cistern was missed, and if so, the decompression may have re-established free communication between this cistern and the other basal cisterns.

Case 4.—*Female, aged* 40. *Headache. Vomiting. Right otitis media. Mastoid operation. Mental dullness and confusion. Papillœdema absent. Exploration posterior fossa. Collection of cerebrospinal fluid in front of right lobe of cerebellum. Complete recovery.*

Mrs. M. D., aged 40, was admitted to the Royal Victoria Eye and Ear Hospital, Dublin, on June 25, 1936, under the care of Mr. T. O. Graham.

In April she had a discharge from the right ear, which lasted about a week and stopped spontaneously. About the beginning of June she began to suffer from headaches which gradually increased in severity and later were accompanied by attacks of vomiting. She felt sick and weak and was unable to work. During this time the discharge from the right ear appeared again, lasted a few days, and stopped without affecting her general condition.

June 25: The right ear appeared normal. There was some tenderness over the right mastoid region. She complained of severe headache, pain in the neck and dizziness. The patient was dull and non-co-operative. There was slight stiffness of the neck and she kept her head turned to the left. The fundi were normal and the fields full to rough tests. She could move the eyes to both sides, but could not hold them in position. There was no nystagmus. Corneal reflexes were normal. The right arm seemed weaker than the left. Arm and leg reflexes were present and equal, and the plantar responses were flexor. The patient said that she had staggered to the right, but as she was too weak to get out of bed this statement could not be checked.

June 27: She complained of severe pain in the right side of the neck and the top of the head. The neck was very stiff. She felt that she was moving to the left side. Any attempt to make her fix her gaze failed. She vomited everything she took. The right mastoid antrum was opened, but it and the neighbouring bone were quite healthy.

June 29: I was asked to see the patient. She was thin and pallid, very apathetic and listless, with slow cerebration and slow speech. There was no papillœdema. She cried when an attempt was made to turn her head. It was impossible to get her to co-operate in any way, although she appeared perfectly conscious. A diagnosis of a right cerebellar abscess was made and she was transferred to the Richmond Hospital.

June 30: Operation. Local anæsthetic. The right cerebellar hemisphere was exposed. It did not bulge into the dural opening and pulsation was present. A needle was passed through the cerebellum towards the mastoid and fluid began to flow freely from it. Four ounces were aspirated and fluid still dropped from the needle. We had the impression that fluid could be obtained as long as the needle was left in position. The cerebellum at this stage had fallen away from the dura and there seemed to be abundance of room in the posterior fossa. The wound was closed without drainage.

Pathological report: "This fluid has all the features of normal cerebrospinal fluid and contains a trace of blood. Protein 20 mg. Cells, monocytes 2 per mm. Faint trace of globulin in Nonne-Apelt test. Sugar normal. Chlorides normal (730 mg.). No organisms seen. Sterile on culture."

The patient vomited during the next two days, but she had no headache nor pain and her mental dullness had disappeared. From this date recovery was uninterrupted and complete. She was discharged on July 16, 1936.

Comment.—As more fluid was obtained than the posterior fossa could accommodate without evidence of gross tension, it is probable that there was a free communication between the cisterna pontis and the rest of the subarachnoid space, and that lumbar puncture might have been as effective as local removal of fluid.

Case 5.—Male, aged 22. Bilateral otitis media. Left mastoid operation. Headache and rigidity of the neck. Papillœdema. Nystagmus. Operation: internal hydrocephalus and a collection of cerebrospinal fluid in front of the left lobe of the cerebellum. Death fifteen days after. Internal hydrocephalus.

J. D., a man, aged 22, was admitted to a Dublin Hospital on November 2, 1935, suffering from double otitis media. About one hour after admission he became semiconscious. As he resented pressure on the left mastoid but not on the right it was decided to operate on the left side. Pus was found in the mastoid and a radical mastoid operation was performed. There was no indication of infection of the lateral sinus or of the dura. After the mastoid operation the patient recovered apparently completely and left hospital on November 27.

On December 4 the patient complained of pain in the back of the head and of pain and stiffness of the neck. When he was readmitted to hospital he had severe occipital headache and some rigidity of the neck. There was complete left facial palsy. The abdominal reflexes were brisk. The fundi were normal and the ocular movements full, but there was marked coarse nystagmus on looking to the left. Left pupil reacted to light more briskly than right.

December 12: Left vestibulotomy was performed on account of the nystagmus, but no improvement occurred. A few days later definite papillœdema of both discs with swelling of about 4D was found. His general condition became steadily worse and the diagnosis of a cerebellar abscess was made.

December 22: I saw the patient for the first time. He looked extremely ill and was dull and stupid. He had intense headache; his neck was rigid and he vomited on the slightest movement.

Under local anæsthesia a needle was passed into the uppermost part of the left ventricle. The fluid spurted from the needle but was immediately checked and allowed to flow slowly. Over 20 c.c. escaped before the tension was relieved. The diagnosis of a lesion in the posterior fossa, probably an abscess, was confirmed by this demonstration of a dilated ventricle. The left cerebellar hemisphere was then exposed under local anæsthesia. The hemisphere was closely applied to the dura in spite of the relief of tension above. There was no subarachnoid fluid over the region exposed. A needle was passed into the hemisphere but no pus was found. It was then passed through the hemisphere towards the mastoid and fluid under tension escaped. Some of the fluid was lost but 50 c.c. were collected. When it ceased to flow the wound was closed without drainage. The patient's headache was immediately relieved. The fluid was normal cerebrospinal fluid. I did not see this patient again. He improved steadily until December 30, when there was a definite reduction in the papillœdema, which measured only 2D. On that date there was a return of headache and a needle was passed into the posterior fossa without result. The ventricle was not tapped nor was a lumbar puncture done. He gradually got worse and died on January 6, 1936.

A post-mortem examination revealed marked dilatation of the lateral ventricles with fine fibrinous adhesions in the region of the foramen of Magendie. The arachnoid membrane was not opaque nor thickened. There was no abscess. The posterior cranial fossa was normal.

Comment.—Repetition of the ventricular tap would have saved this patient for a time, and an opening between the fourth ventricle and the cisterna magna would probably have given him permanent relief. Lumbar puncture would have been dangerous and useless.

Case 6.—*Male, aged* 20. *Right otitis media and mastoiditis. Mental symptoms. Radical mastoid operation. Excess of cerebrospinal fluid over cortex and in ventricles. Progressive deterioration. Terminal streptococcal infection. Internal hydrocephalus found at autopsy.*

The patient, a skilled artisan, aged 20, complained of pain in the right ear on June 26, 1936. Next morning a discharge from the ear relieved the pain. On June 29 the pain returned and he was admitted to the Royal Victoria Eye and Ear Hospital, under the care of Mr. T. O. Graham.

On admission temperature was 104° F., pulse 122, respirations 22. There was a perforation in the upper part of the membrana tympani with inflammation below and in front. The lower part of the drum was punctured and pus escaped.

A few days later he became delirious during the night, took the dressing off and tried to get out of bed. There was no pain in the right ear or tenderness over the mastoid. The abdominal reflexes were active, the knee-jerks present and the plantar reflexes flexor. His neck was not rigid and Kernig's sign was not present. He did not vomit and the discs remained normal. No dysdiadochocinesia or past-pointing. The pupils were equal and reacted normally. There was no nystagmus. On lumbar puncture the pressure was 30 mm. water. The fluid was clear and contained no cells, and the globulin was not increased.

July 3 : He was "strange," got out of bed and tried to evict other patients from their beds and get in himself. There was no discharge from the ear and no pain.

When questioned the relations said that the patient's temperament had changed in the last month and that he had become irritable. A fortnight before admission he complained of headache. When I saw him on July 3 he was quiet but disoriented in space and time, and his face was expressionless. He said "It is what God said would happen." He quoted the Bible about "God's treatment of sinners" quite coherently, but then wandered off to another subject. He did not seem to have any pain. His fundi were normal. There was a free purulent discharge from his right ear. Later he became very restless and violent but after an injection of luminal he was clearer mentally, but he refused to speak except to give his name. He moved all his limbs freely. The patient's condition did not suggest increased intracranial pressure.

July 7: Dr. Graham opened up the mastoid antrum, and found pus all through the mastoid process. The dura and the lateral sinus were exposed and appeared normal. As there seemed to be enough infection to give rise to a toxæmia which might account for the mental state of the patient, it was decided to do nothing further.

July 9: Temperature normal and pulse 100. He was stuperose and his neck was slightly stiff. No difference was observed between the tone of the limbs. The left knee-jerk was brisker than the right, but the plantar responses were flexor and the abdominal reflexes present and equal. His right eye was constantly turned to the right. The left disc was healthy, the right was not seen.

July 10: Operation. A small opening was made over the right frontal lobe. When the dura was opened, thickened opaque arachnoid bulged into the opening. This was punctured and a free flow of cerebrospinal fluid appeared. The anterior horn of the right ventricle was punctured with patient's face upwards. Fluid flowed in a gentle stream from the needle and altogether over 20 c.c. of fluid were removed, most of it by aspiration without moving the head. It was concluded that there was an internal hydrocephalus and that there was no supratentorial abscess on that side. The right lobe of the cerebellum was then exposed. There was no tension whatever and exploration failed to reveal anything abnormal either in the cerebellum itself or in its neighbourhood. No fluid was obtained by passing the needle right through the cerebellum in the direction of the petrous bone. Next day he was better, but on the following day right divergent strabismus and nystagmus developed.

July 13: He appeared somewhat clearer and was less restless. There was right divergent strabismus and constant nystagmus with the quick movement upwards and outwards to the right. Abdominal reflexes not so marked on the left side as on the right. He succeeded in getting the dressing off to-day. He recognized his mother and answered questions occasionally, with some degree of dysarthria.

July 14: He was more rational, recognized and named a pen but was extremely restless, or he lay silent, his eyes following every movement. Nystagmus was not nearly so marked. The fundi were normal. An attempt to tap the right ventricle failed. During the next few days he improved and spoke coherently and sensibly. Temperature remained normal and pulse-rate steadily dropped from 150 to 100.

July 19: Temperature rose suddenly in the evening. His mental state was clearer. There was no change in the reflexes, but nystagmus was still present. On lumbar puncture the pressure was 85 mm., the fluid was clear, chlorides 720 mg., protein 18: no cells were seen and cultures were sterile.

July 21: Quite normal and bright mentally and he talked rationally. Temperature, pulse and respirations normal, but in the evening his temperature rose to 102° F. Next day he had a rigor; temperature was 102·4° F. and pulse 140. He did not complain of headache and was quite clear and intelligent, though a little slow in answering. There was some dysarthria. The mastoid wound discharged freely. The squint of his right eye had disappeared and both eyes moved readily. No nystagmus was observed. His neck was freely movable and there was no tenderness along the jugular vein. The right arm sagged, the right grip was weaker than the left, and the finger-nose test was not so good on the right side. The abdominal reflexes were present and active, but the knee-jerks were feeble.

July 23: He was very confused and delirious: said "I'm going to hell"; "I'm Esau because I'm a hairy man." "My hands were never as clean as that before." He answered questions well. The neck was more rigid but the nystagmus was less. The left ventricle was tapped; there was excess of subarachnoid fluid and the arachnoid was thickened and gelatinous, obscuring the cortex. The ventricular fluid flowed freely at first, 20 c.c. were aspirated. The right ventricle could not be found. There was no tension on the flap.

July 27: The temperature came down to normal, but the pulse-rate increased to between 140 and 150 and the respirations to about 40. It was necessary to feed him by a nasal tube. He seemed to be quite conscious but did not speak. He was very wasted. On the following day a corneal ulcer had developed on the right side, and this side of the face seemed insensitive to pin-prick. The conjunctival and corneal reflexes could not be obtained. A needle was passed into the right ventricle and about 10 c.c. of blood stained fluid were obtained, the patient being face up the whole time. A spontaneous nystagmus appeared immediately after the removal of the fluid and the patient reacted by moving his head, but he did not speak. The fluid contained hæmolytic streptococci. The patient died.

Post mortem.—Cortical meningitis limited to the frontal region. Internal hydrocephalus.

Comment.—The excess of subarachnoid and ventricular fluid without tension suggested cerebral atrophy, which was also suggested by his mental condition. It is probable that the otitis media was not in any way responsible for the intracranial condition. The terminal meningitis was probably caused by one of the ventricular punctures through a wound contaminated by the patient's hands. The case is included because at the beginning otitis media seemed to be the primary lesion.

Classification According to the Operative Findings.

In Case 1 the absence of pressure on lumbar puncture and on ventricular puncture, and its presence in the posterior fossa seem to exclude a communicating hydrocephalus and to allow this case to be classified as one of a localized cystic collection of cerebrospinal fluid in the posterior fossa.

A similar diagnosis is justifiable in Case 2 because of the similarity of the operative findings.

These two cases differ markedly from most of the cases of cystic collections in the posterior fossa previously reported. In the latter the encysted fluid was under gross tension, issuing from the needle in a strong jet and sometimes striking the assistant in the face; but in these cases the tension of the fluid was but slightly increased and yet removal of the fluid relieved the symptoms.

In Case 3 the ventricular pressure was never increased, but the spinal pressure was 200 mm. water on one occasion, while some degree of tension in the posterior fossa and of interference with the circulation of the cerebrospinal fluid may be inferred from the result of the cerebellar decompression.

In Case 4 the fact that much more fluid was withdrawn than could conceivably be retained in the posterior fossa without gross tension, suggests the presence of a communicating hydrocephalus.

Case 5 had a localized collection of fluid in the posterior fossa and an independent internal hydrocephalus. The fluid in the lateral ventricle was under extreme tension, and that in the posterior fossa, though tapped immediately after the ventricular puncture, showed tension no less extreme.

Case 6 would appear to be one of otitis media occurring in a patient with compensatory hydrocephalus.

The operative findings were confirmed by post-mortem examination in cases 5 and 6, but whether they disclosed the actual conditions present in the other cases is doubtful. For instance, cerebrospinal fluid may be obtained in the subarachnoid space behind the petrous temporal bone in some perfectly normal cases, in those with communicating or external hydrocephalus and in those with localized cystic collections. The amount and tension of the fluid withdrawn and the result of its withdrawal may suggest one rather than another of these conditions, but anatomical verification may be impossible.

In the following table the conditions suggested by the operative findings are presented along with the outstanding symptoms and signs.

No general conclusions can be drawn from this table except, perhaps, that headache and vomiting occurring in the course of otitis media may indicate any sort of derangement in the amount or circulation of the cerebrospinal fluid. These derangements fall into two general types: (1) A general excess of cerebrospinal fluid in freely communicating ventricular and subarachnoid systems, the so-called communicating or external hydrocephalus. (2) Cerebrospinal fluid encysted in the ventricles or in some part of the subarachnoid pathway, that is obstructive internal hydrocephalus or localized collections of fluid in the posterior fossa. From a practical point of view intracranial abscess may be included in the second type, for it is the fact of localization that is important rather than the nature of the fluid localized. Whether it be cerebrospinal fluid or pus that is localized a local operation for its removal is necessary.

Presumed condition	Case	Looked	Headache	Vomiting	Papilloedema	Cerebral symptoms	Nystagmus	Pressure L.P	Pressure V-P.	Pressure posterior fossa
Localized cystic collection of fluid in posterior fossa	1	Well	+		+		+	90 mm.	Not increased	Slightly increased.
	2	Well	+	+			+	—	—	Slightly increased.
,,	3	Well	+	+				200 mm.	Not increased	Slightly increased.
Communicating hydrocephalus	4	Ill	+	+		Confusion		—	—	Slightly increased.
Obstructive hydrocephalus and localized collection (verified)	5	Ill	+	+	+	Slow cerebration	+	—	Greatly increased	Greatly increased
Compensatory hydrocephalus (verified)	6	Ill				"dementia"		80 mm.	Not increased	Not increased.

The condition verified in Case 5 indicates that lumbar puncture might be as dangerous when there is no abscess as it is when an abscess, especially a cerebellar one, is present. On the other hand, in the first type of case, that of communicating hydrocephalus, lumbar puncture is both safe and curative.

It is doubtful whether cases of the first type can be distinguished infallibly from those of the second, including abscess, on clinical evidence alone. Ventricular puncture is safe in cases of either type and it gives information that lumbar puncture cannot give. When the arachnoid is opened an excess of subarachnoid fluid would indicate an external and probably a communicating hydrocephalus. If only a few c.c. of fluid be found in the ventricle any local collection of fluid is probably to be found above the tentorium, usually in the temporal lobe. Case 1 shows that a small ventricle does not exclude a collection of fluid under tension in the posterior fossa.

If over 25 c.c. of fluid be obtained from the uppermost ventricle without manipulation of the head the presence of an internal hydrocephalus, either encysted or secondary to an expanding lesion in the posterior fossa, can be assumed, in which case the posterior fossa should be explored. In every case in which examination of the cerebrospinal fluid shows any increase in the number of cells or in the amount of protein, it is probable that an intracranial abscess is present, although a normal fluid by no means excludes an abscess.

All these procedures can be carried out readily under local anæsthesia, and by them a differentiation between cases of type 1 and type 2 can usually be made. There are many more cases of the second type than of the first, for the second type includes abscess. It is recognized that an accurate clinical diagnosis of the situation of an abscess can be made in the majority of cases, and that ventricular puncture may not be necessary, and it is better to localize an abscess by other means than by putting a needle into it. Ventriculography is sometimes advisable. The above routine is suggested only for cases in which localizing symptoms are absent or equivocal.

Terminology.—The terms in this paper are used in their ordinary textbook sense. The term "hydrocephalus" means only an increase in the volume of the cerebrospinal fluid within the skull, but in common usage it implies dilatation of the ventricles. Such dilatation is usual but is not constant, especially in communicating hydrocephalus.

Localized cystic collections of fluid in the posterior fossa have been attributed to adhesions occluding part of the subarachnoid space. All otologists are familar with this condition and many cases have been reported under the name of meningitis serosa circumscripta or cystic arachnoiditis. Bourgeois [2] gives abstracts of the cases reported by the following: Baldenweck [3], Bárány [4], Jenkins [5], Kobrak [6], Lewy [7], Moulonguet and Anglade [8], Mygind [9], Jacobsen [10], Lemaitre and Aubin [11], Vincent [12], Wylie and Watkyn Thomas [13]. It has not been possible to consult the original reports in every instance.

The encysted fluid is usually described as normal cerebrospinal fluid, without any increase in the number of cells or in the amount of protein. For this reason Bourgeois regards the condition as a local increase in the volume of the cerebrospinal fluid, and therefore as a type of hydrocephalus. He adopts the term "otitic hydrocephalus" to designate any excess of cerebrospinal fluid occurring in association with otitis media. Symonds had already introduced this term, but he had excluded localized cystic collections of fluid from its application.

As any sort of derangement in the amount or circulation of the cerebrospinal fluid may occur in association with otitis media, it seems desirable to use the term "otitic hydrocephalus" in the wide sense suggested by Bourgeois.

Conclusion.—In cases of otitis media it is sometimes difficult to be certain whether an abnormality in the amount or circulation of the cerebrospinal fluid is present or not. If an abnormality be present it is important to determine its type, for in some types lumbar puncture is dangerous.

I would like to express my indebtedness to all those who gave me the opportunity of studying the cases on which this paper is based.

BIBLIOGRAPHY.

[1] Symonds, C. P. *Brain*, 1931, **54**, 55.
[2] Bourgeois, R. "Les Hydrocephalies," Paris, 1935.
[3] Baldenweck, L. *Rev. d'Oto.-Neuro-Ocul.*, 1925, **3**, 746.
[4] Bárány. In "Thèse de Georgopoulos" (*Thèse de Paris*, 1928).
[5] Jenkins. *Journ. of Laryng. a. Otol.*, December, 1926, 781.
[6] Kobrak. *Zeitschr. f. Hals. Nasen u. Ohren*, **14**, 137.
[7] Lewy. *Zeit. f. Klin. Med.*, 1931, —, 38.
[8] Moulonguet, A., and Anglade, L. *Rev. d'Oto.-Neuro.-Ophth.*, 1934, **xli**, 513.
[9] Mygind. *Monatschr. f. Ohren.*, 1920, **54**, 984.
[10] Jacobsen, C. *Ibid*, 1917, **51**, 374.
[11] Lemaitre and Aubin. *Arch. d'O.-R.-L.*, 1925.
[12] Vincent. Communication included in "Les Hydrocephalies," Bourgeois, p. 121.
[13] Wylie, A., and Watkyn Thomas, F. W. *Journ. of Laryng.*, 1927, **42**, 824.

THE SYNDROME OF THE SUPERIOR CEREBELLAR PEDUNCLE IN THE MONKEY.[1]

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I.—INTRODUCTION.

DISORDERS of movement arising from damage to the cerebellum are easily recognized, but the mechanisms whereby the cerebellum maintains a co-ordinating rôle in muscular activity remain obscure. Even the neural pathways by which the cerebellum receives and transmits impulses to other parts of the central nervous system are imperfectly known. It is generally agreed that in the inferior and middle peduncles fibres carrying afferent impulses predominate and that the superior cerebellar peduncle contains the great efferent systems of the cerebellum. The present report is concerned with the disturbances of posture and movement following isolated division of one or both superior cerebellar peduncles.

(1) *Historical Review.*

Ferrier and Turner [2] were the first investigators to attempt section of the superior cerebellar peduncle in the monkey. They studied three macaques after unilateral section of the brachium conjunctivum. In two of these disturbance of equilibrium was marked. When attempting to walk the animals deviated and fell to the side of the lesion; the ipsilateral limbs were raised high and wide of the body. Fine tremors, which became amplified on exertion, were present in the ipsilateral extremities. In one animal nystagmus was present and increased on looking to the side of the lesion. These two experiments were terminated at thirty and forty days: the third animal died five days after operation.

Keller and Hare [4] in 1934, using dogs, cats and monkeys, partially divided the mesencephalon at the level of the inferior colliculus. They did not find any correlation between the degree and duration of ataxia and the extent of the damage to the brachium conjunctivum. They concluded (p. 1271): "It is not essential that a brachium conjunctivum be intact for normal homolateral co-ordination of muscular movements and static muscular stability."

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Recently Ferraro and Barrera [1] have reported the results of section of the superior cerebellar peduncle. Their lesions were made from within the fourth ventricle. They found that incomplete unilateral lesions resulted in "ipsilateral dysmetria with more or less hypotonia and hyporeflexia." Following bilateral lesions the same symptoms occurred on both sides, lasting only a few weeks. In one case they considered that a complete and uncomplicated lesion of the superior cerebellar peduncle had been made. Rolling movements, and spiralling toward the side of the lesion on jumping, together with nystagmus toward the opposite side, complicated the usual findings after incomplete division of the superior cerebellar peduncle. The results obtained by these authors following section of the superior cerebellar peduncle were not constant and they were unable to describe a definite syndrome.

(2) *Definitions.*

Certain terms used to describe the signs of cerebellar deficit are often employed loosely. In order to avoid ambiguity these terms will be briefly defined: the definitions given by Gordon Holmes in his Croonian Lectures [3] have been followed in large measure.

Cerebellar ataxia is a term used to embrace all abnormal motor phenomena of cerebellar deficiency, including dysmetria, tremor, decomposition of movement, &c.

Dysmetria is taken to include any disturbance in the range of voluntary movements.

Hypermetria is excessive range of movement as when the limb overshoots the desired point.

Hypometria is deficient range so that the limb stops before the goal is reached. Frequently a concomitant factor is a disturbance of the force of the movement which is not well adapted to its end.

Decomposition of movement represents the performance of an act so that "the various components of the act are not performed in their proper sequence or measure" [3].

Tremor may be classified as that occurring in an extremity at rest or maintaining a posture ("static tremor"), and that occurring during any part of active movement ("kinetic tremor"), and in any plane. Terminal tremor, i.e. the tremor occurring at the end of a movement is usually more marked than the tremor at the start or during the course of a movement.

Tone (*tonus or postural resistance*) is applied by the clinician [3] "to that slight constant tension characteristic of healthy muscles, owing to which the limbs, when handled or moved passively, offer a definite resistance to displacement." To the physiologists "tone" is a reflex postural contraction most evident in anti-gravity muscles, the degree of postural contraction in any given muscle depending upon the position of the body in space at the time of examination.

"*Hypotonia*" is a somewhat unsatisfactory but widely-used term denoting a diminished resistance to passive movement; the passive movement of a hypotonic limb may be carried through a range greater than normal, and on passively shaking of the proximal segment of a "hypotonic" limb there is abnormal excursion at the affected joint.

(3) *Methods of Examination.*

At each examination the animal was observed both in his cage and running about a long corridor; then a neurological examination was carried out. Hemianopsia was tested for by noting the reaction of the animal to an object rapidly brought into its peripheral field of vision. The external ocular movements were noted as the animal looked around at various objects. The condition of the remainder of the cranial nerves was determined by inspection. The tendon reflexes routinely elicited were the triceps, biceps, radial, ulnar, knee and ankle jerks. The plantar response was obtained by stroking the lateral surface of the sole of the foot with a blunt object, usually a pencil. Motor function was estimated by watching the animal walk, run, and climb and noting the strength of the grasp and the resistance encountered in handling the animal. Voluntary movements were further studied by observation of feeding and the ability of the animal to walk on a ledge 1½ in. in width. In some cases the animal would reach for food from the observer's hand, when the degree of co-ordination of the upper limbs could be accurately determined.

Observation of these animals in small cages did not give an adequate picture of their motor function, for by various tricks the animal concealed deficiences of movement and equilibrium. Only when the animals were obliged to use the affected limbs were these irregularities revealed.

Running about a long corridor brought out some latent abnormalities. To bring out the maximum deficit in motor performance the flexor tendons were sectioned in the wrist contralateral to the divided superior cerebellar peduncle in several cases. The animal was thus compelled to use the affected hand for feeding, and the deficiency revealed after some of these sections was astounding. The following is a direct quotation from notes made on a macaque monkey which had its left superior cerebellar peduncle sectioned forty-three days previously (S.P. 24).

" The left limbs are used very little in purposeful volitional movements and the range of these movements is quite small. Accordingly there is little ataxia to be noted when the animal moves the individual extremities. The right extremities are always used for picking up food and the left are only used in steadying the object as it approaches the mouth. In these movements there is no ataxia, only a slight unsteadiness. . . ."

Under ether anæsthesia that morning the flexor tendons of the right wrist were sectioned. That evening the animal showed a very definite ataxia and tremor upon reaching for objects. Four days later, when all effects of anæsthesia must have passed, the animal was described as follows:—

" Last night upon reaching for an object the movement of the left upper extremity was definitely jerky, usually the animal missed the object, striking the floor on either side of it, then corrected. A slight fumbling occurred after which the animal grasped the object and then carried it to his mouth. Just as the hand was about to reach the mouth usually a fine tremor occurred, then the object was placed in the buccal cavity. Such is the usual sequence of events. This morning watching it again reaching for a peanut it was noticed that at times the left upper extremity shot up too high and too far for the object."

Because an animal is able to conceal a motor disability so effectively the progress of these animals has been watched critically.

Resistance to passive movement was determined by manipulation of the extremities by gauging the resistance encountered on fully flexing or extending a joint. The range and rate of flopping of the hand and foot were observed on shaking the proximal segment of the arm and leg respectively.

The pilomotor response was obtained by massaging the base of the neck, or exciting the animal. Vasomotor changes were determined by feeling the temperature of comparable limbs.

(4) *Material and Technical Procedures.*

Animals.—The experiments were performed upon a series of twenty-five monkeys. Three died within a week as a result of operative trauma and two were used for acute experiments within ten days. One animal escaped from the colony twenty-eight days after operation. Three animals were used as controls and in these the entire operative procedure was carried out but the peduncle was not sectioned. Three were used for Marchi degeneration and were sacrificed ten to twenty days after operation. Three animals lived from three weeks to three months after operation and ten for more than three months. In all, one or both superior cerebellar peduncles were sectioned on twenty animals. Partial sections were made on two animals. Excluding the five that did not survive ten days, and the one which escaped, this report is based upon the results of section of one or both superior cerebellar peduncles n nineteen monkeys, three of them baboons (*Papio papio*) and sixteen macaques (*Macaca mulatta*). The syndrome in the baboon was practically the same as that in the macaque monkey and hence they are grouped together.

Operative procedures.—All operative procedures in this series were carried out in the Laboratory of Physiology, Yale University School of Medicine. Sodium amytal or nembutal was used as anæsthetic for all intracranial procedures, and the usual precautions were taken to ensure asepsis. A few minor procedures were performed under ether anæsthesia. Following cleansing of the scalp in the usual manner a large posteriorly situated osteoplastic flap was turned down, and the dura opened to expose the cortex of the occipital and parietal lobes. With a fine scalpel the arachnoid was incised to allow the cerebrospinal fluid to drain and thus provide additional space within the intracranial cavity. The occipital pole was then elevated and the usual small vein or two draining into the lateral sinus coagulated and divided. This manœuvre brought into view the tentorium lateral to the mid-line and as far as its anterior margin, and when followed by its reflection laterally, exposed the superior surface of the cerebellum. The arachnoid over the anterior portion of the cerebellar hemisphere was incised with the cutting current, releasing the spinal fluid of the cisterna ambiens. At the same time small vessels which occasionally pass from the anterior margin of the cerebellum, and which may cause persistent bleeding, were coagulated. Using a cotton pledget to protect the cerebellum, it was then possible to retract the anterior margin of the hemisphere from the colliculi and bring into view the superior cerebellar peduncle. With a sharp iridectomy knife the latter was sectioned just before it entered the brain-stem. If this was carefully done no bleeding occurred. The tentorium was replaced but not sewn, and the occipital lobe allowed to fall back over the posterior fossa. Using the above precautions in almost every case the dura was closed without difficulty. The bone flap was replaced and skin sutured in the usual manner in anatomical layers.

Anatomical controls.—The histopathological technique for the anatomical control of these cases was carried out in the Neurological Laboratory of Professor B. Brouwer at Amsterdam, Holland, by one of us (A.E.W.) who wishes to express his appreciation for the facilities which were placed at his disposal. Every case included in the present report has been histologically verified. In five cases serial sections through the cerebellum and mesencephalon were cut and every twenty-fifth section stained according to the Nissl technique. In three cases the brains were treated according to the Marchi technique and sectioned serially, every fourth section being mounted. In one case, in which the cerebellum was subsequently removed, the latter was sectioned serially, stained by Nissl technique and the cells of the dentate nucleus examined for retrograde changes in order to determine the completeness of the peduncular section. In one case serial sections of the site of the lesion were made and stained according to the Weigert-Pal method for myelin. In the remaining cases blocks, slightly posterior to the inferior colliculus have been cut and stained for myelin to verify the lesion. Further anatomical control of these last cases (serial section of the lesion and cerebellum) is being carried out at the present time. The myelin sections present clear evidence of the extent of the lesion of the peduncle by reason of the absence of myelinated fibres or a clear area in the usually darkly staining area occupied by the brachium conjunctivum.

II.—The Syndrome Following Unilateral Section of the Superior Cerebellar Pedunicle.

(1) *Immediate effects.*

Day of operation.—Usually the animal recovered consciousness within six hours after operation. In attempting movement at this time, it was very unsteady and swayed or fell from side to side in the cage. If offered food, it reached with the upper extremity on the side of the lesion. The movement was accompanied by a wild tremor and usually the food was knocked away some distance, or if a dish of water was the goal, it was spilt.

In a few cases there was a coarse nystagmus in both eyes on looking to the side of the lesion, but some animals showed no nystagmus even at that time. No weakness in any muscle group was apparent in any part of the body. Only two animals were examined at this time. They showed no significant change in the resistance to passive movements in any group of muscles.

First post-operative day.—By the first post-operative day the animal had recovered from the effects of the anæsthetic and was no longer drowsy. It squatted in the corner of the cage, holding on to the wire netting with one (usually that contralateral to the lesion) or both hands. It did not move about the cage, but when disturbed swayed unsteadily from side to side. In a few cases there was a spontaneous nodding tremor of the head for a day or two. When the animal attempted to walk or run about, it staggered and fell, usually to the side of the lesion. In progression the animal did not raise its buttocks from the floor. The hind limb on the side of the lesion frequently gave way beneath the weight of the animal. Progression was accomplished by alternately flinging the fore limbs well forward and shuffling along with the hind ones. Even this frequently caused the animal to fall to the affected side, necessitating wild movements of the limbs to right itself.

An occasional animal had a homonymous hemianopsia in the fields of vision contralateral to the lesion. When present it usually disappeared within a week. A few animals had a slow, coarse horizontal nystagmus on looking to the side of the lesion. This, however, never lasted longer than forty-eight hours, and usually there was no other cranial nerve involvement. Occasionally the 4th nerve was damaged, producing an internal strabismus and some weakness of the ipsilateral eye in downward and outward gaze.

The tendon reflexes were in general sluggish, but about the same on both sides. In a few animals the contralateral knee-jerk was increased somewhat for a few days post-operatively. In some cases the knee-jerk on the ipsilateral side temporarily took on a pendular quality. The responses to plantar stimulation on both sides was either absent or flexor in type. Pin-prick response was equally poor on the two sides.

Although the ipsilateral hind-leg did not support the body adequately in walking, no motor weakness could be detected on examination.

Usually the animals favoured the ipsilateral extremities during the first post-operative day. When these were used to reach for food a severe tremor developed, the limb, oscillating through a range of 4 to 5 cm., often dislodging the desired object. The food was carried unsteadily to the mouth, and the hand frequently shot past the mouth or struck it so hard that the object was knocked to the floor. When this did not occur, there was a marked oscillatory tremor persisting until the animal dispósed of the morsel. Movements of mastication were normal.

Examinations were made to determine the resistance to passive movements in the different muscle groups at frequent intervals following operation. Usually the ipsilateral limbs were less resistant to passive movements at all joints and were more floppy than the contralateral extremities. In some animals, however, no decrease in resistance was detected. Within a few days there was no difference in the resistance to passive movement of the joints of the two sides, save in an occasional animal. Accordingly, decreased resistance to passive movement or "hypotonia" was not an outstanding sign in this series.

In the ipsilateral limbs placing and hopping reactions were disturbed temporarily, but within a few days there was no difference between the two sides. In spite of repeated examinations for vasomoter changes in these animals, none was detected.

In about half the cases a definite paresis of piloerection was noticed on the ipsilateral side of the trunk. It was difficult to detect any difference in the extremities. This would appear to be the result of involvement of neighbouring structures of the brain-stem and not due to the section of the superior cerebellar peduncle.

At rest in the squatting position, even on the first post-operative day, the animal assumed a normal general posture except that a tilt of the head caused the eye ipsilateral to the lesion to be slightly higher than the contralateral eye. At rest in the squatting or sitting position, the posture of the extremities was not symmetrical but the limbs did not assume markedly abnormal positions. During the first few post-operative days the animal walked with the buttocks almost scraping the floor and the affected side juxtaposed to the wall. Even with this support it fell frequently. This was aggravated by the unsteadiness of the semiflexed ipsilateral hind limb. When the animal was able to walk without support, the disturbance in gait was even more marked. The base was definitely wide on the side of the lesion. The normal rhythm was disturbed because of the irregularities in range and direction in the movements of the ipsilateral limbs. The stride was further interrupted by the variable force of the movements of progression. This either threw the animal high to one side or failed to support the body adequately. Because of the disturbance of the ipsilateral extremities, the hind limbs did not track well, but deviated to the side of the lesion so that the animal came to run sideways. These irregularities in gait gradually improved and in approximately two weeks the animal was usually able to run about without falling, although the stride was still irregular in both rhythm and force, and the base definitely widened.

(2) *Late Effects.*

Within a few weeks of the operation the acute signs subsided and after a period of six weeks there was but little change from day to day. The head remained slightly tilted to the side contralateral to the lesion. No motor weakness was apparent and the tendon reflexes were moderately active on the two sides. The intention tremor in the ipsilateral upper extremity was minimal, and usually masked by the disinclination of the animal to use the limb and the deliberate manner in which it was employed. There was no significant difference between the resistance to passive movement in corresponding muscle groups on the two sides of the body, nor was there any hypotonia. The gait still showed a definite but slight irregularity. The base was widened on the side of the lesion. The stride, while regular, was not as smooth as that of a normal animal, and one could still detect a trace of high-stepping and unsteadiness of the movements of the ipsilateral limbs. When walking a narrow ledge the ipsilateral limbs occasionally missed, and not infrequently were awkwardly placed, and then corrected. The animal showed hesitance in placing the ipsilateral limb upon the ledge and not infrequently refused to use the hind limb in this test. This minimal deficiency in gait, and an unsteadiness of the ipsilateral fore-limb in voluntary movement, persisted as long as any animal was observed (in one case seven months).

Experiment 1.—*Section of the left superior cerebellar peduncle*: *marked ataxia of the ipsilateral extremities gradually decreasing* (*S.P. No.* 15).

Operation.—The subject of this experiment was a normal immature male, *Macaca mulatta.* On February 12, 1936, under sodium amytal anæsthesia the occipital lobe was elevated after division of two small veins passing from the cortex to the lateral sinus. The left superior cerebellar peduncle was sectioned with a sharp iridectomy knife following the exposure described above. No bleeding was encountered and the exposed cerebellar tissue appeared to be uninjured.

Post-operative notes.—First day: The animal sat in the cage clinging to the bars. Although its motor activity was slow, each movement was jerky and tremulous. At rest, there was no tremor of the body or extremities but occasionally a fine nodding tremor of the head was apparent. The visual fields appeared to be full. The animal had a full range of external ocular movements and no nystagmus upon looking in any direction. Facial movements were full on the two sides. The tendon reflexes were equally sluggish on the two sides; stimulation of the plantar surface of the feet evoked no response. The animal preferred to use the left upper extremity in reaching for food. Such a movement provoked a marked oscillatory tremor of the limbs so that frequently the morsel was knocked away. Once grasped, the food was carried to the mouth with relatively little unsteadiness except for terminal tremor.

No paresis or paralysis could be demonstrated. There was no definite abnormality in the resistance to passive movement of any joint, although at times there seemed to be less resistance in all muscle groups of the proximal joints of the right extremities than in those of the left extremities. The animal was unable to walk or run. Such an attempt resulted in wild swaying and falling to either the right or left side. Pin-prick appeared to be appreciated equally on the two sides.

Second day: In the cage the animal squatted in one position for long periods without moving, but did not cling to the wire. At rest the head was slightly tilted to the right so that the right eye was lower than the left, and there was no tremor of the head or of any part of the body.

Examination of the cranial nerves revealed no abnormality. There was no visual defect and no nystagmus. The tendon reflexes remained sluggish; both plantar responses were flexor. There was no paresis of the extremities, although the animal preferred to use the left hand. The marked terminal tremor persisted. There was neither increased nor decreased resistance to passive movement in the extremities. When the animal was persuaded to walk it exhibited a marked unsteadiness, falling frequently to the left and occasionally to the right. Progression was accomplished by alternately flinging the fore-limbs, particularly the left upper extremity, far forward. In this movement the left fore-limb was widely abducted. The hips were but slightly elevated from the floor and the hind legs awkwardly pushed the animal forward. During this, the left lower extremity frequently dragged or gave way, precipitating the animal on its left thigh. Occasionally the left hind limb struck the right, and the animal tripped. At times the left hind limb was placed upon or became entangled with the left fore-limb. The animal never walked upon the dorsum of the foot. When it became excited there was more piloerection on the right side of the back than on the left.

Fifth day: The head was still maintained slightly tilted to the right. Neurological examination showed essentially the same findings as on the second day. The animal still crouched when walking and swayed markedly. The left hind leg frequently gave way, precipitating a fall.

Eleventh day: The gait was improving and the animal rarely fell. The stride was quite irregular and there was a tendency to deviate to the left, owing to errors in the movements of these limbs. There was a suggestion of weakness of the left limbs as compared with the right. A moderate degree of ataxia was still present in the left upper extremity. The remainder of the neurological examination was negative.

Twenty-third day: At rest the animal squatted with the head on a horizontal plane and was able to run about without falling. The left extremities were still unsteady, and high stepping on the left broke the rhythm of the stride. There was a definite tendency for the hind limbs to track to the left of the fore ones. When made to walk a ledge, the left extremities were awkward and missed the ledge every third or fourth time. There was a definite ataxia of the left upper extremity best seen when the animal reached for food. Examination revealed no abnormality of the reflex muscular status or sensation. There was no gross muscular weakness.

Thirty-first day: There was still a marked disturbance in the gait, and some ataxia on voluntary movement of the left upper extremity.

Forty-first day: The animal squatted in a normal position. The head was at times slightly tilted. There was still an irregularity in the stride of the left extremities, and the base was widened on the left side. A slight left-sided paresis of piloerection was present. Hopping reactions were normal, but there was a slight lag in the placing reaction of the left fore-limb.

Sixty-first day: The position of the head was normal. It was difficult to detect any ataxia of the left upper extremity. The irregularity of the stride persisted and the hind limbs tracked to the left of the fore-limbs. When walking a narrow ledge, the left upper extremities did not place precisely.

Seventy-eighth day: The stride was not smooth and even, for the left limbs abducted as the animal ran along, and the left hind leg occasionally hit the right hind-limb. The left fore-limb was sometimes swung too far forward. This hypermetria was only occasionally present. The animal did not fall. When walking along the ledge the left extremities missed approximately once in six trials, and the animal was disinclined to place the left foot on the ledge. Examination of the cranial nerves, reflexes and sensation failed to reveal any abnormality.

Examination revealed no gross weakness of any muscle group. When reaching for objects, there was still some unsteadiness and terminal tremor in the left upper extremity. The tremor was through a very small range and did not exhibit the wide oscillations seen in the more recent post-operative state. There was no difference in resistance to passive movement of any joint in the extremities of either side, but there seemed to be slightly more floppiness in the left wrist than in the right as tested by shaking the limb.

The animal showed no deficiency whatsoever in the placing and hopping reactions of the extremities. Usually the left extremity was placed more quickly than the right.

When the animal became excited there was slight paresis of piloerection on the left side.

Seventy-ninth day: At this time the right superior cerebellar peduncle was sectioned. The syndrome following this, with the anatomical findings, will be presented in the next section of this paper.

(3) *Discussion.*

In monkeys the conspicuous signs of cerebellar deficit which follow unilateral section of the superior cerebellar peduncle diminish rapidly in intensity but never disappear; briefly stated they consist of ataxia, with dysmetria, affecting the extremities predominantly. After a few months scant abnormality is noted in the limited activities of the animal in the cage, but if it becomes excited, fatigued, or forced to use its affected extremities for delicate movements, the cerebellar deficiency is once more manifest.

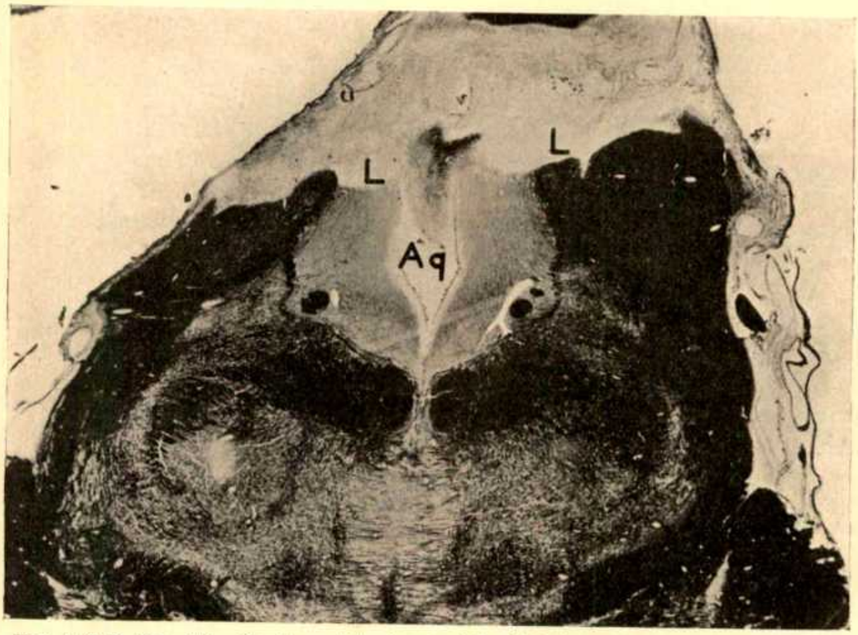

FIG. 1 (S.P. No. 20).—Section at the level of the inferior colliculus from an animal in which the posterior portions of both inferior colliculi were incised to the aqueduct. (Weigert-Pal stain: × 8.)

Section of the superior cerebellar peduncle as performed in the above operation severs the following systems: the brachium conjunctivum (dentato-rubro-thalamic tract), the ventral spinocerebellar tract and the hook bundle. Some of the operations have damaged the dorsal part of the tectum and have undoubtedly injured tracts lying near the superior cerebellar peduncle, such as the spinothalamic, secondary trigeminal tract and reticular bundles from the hypothalamic region. As anatomical examinations of the material has shown, these latter have not been constantly damaged by the lesions, and hence they cannot be considered responsible for the production of the syndrome, which was practically the same in each case. Injury to constituents of the superior cerebellar peduncle seems to be the ætiological factor. The part played in the syndrome by each component of the peduncle has not been analysed in detail, but we are of the opinion that the rôle of the ventral spinocerebellar tract and the hook bundle in the production of the cerebellar signs shown by these animals is not very great, but that interruption of the brachium conjunctivum plays the most prominent part. It is true that some slight damage is done to the anterior margin of the cerebellum at the time of operation, and this requires consideration.

The effect of such coincidental damage to the cerebellum and tectum has been thoroughly investigated. In three animals the entire operative procedure has been carried out with the exception of the section of the peduncle. In each case the peduncle was clearly visible. In none of these cases was there the slightest disturbance within twenty-four hours of operation. In three cases the superior cerebellar peduncle was sectioned after removal of the ipsilateral occipital lobe, thus avoiding appreciable damage to the cerebellar cortex. In one animal an incision was made across the posterior margins of both inferior colliculi; the following day the animal showed no abnormality in gait or motor performance (fig. 1). As an added control in one animal the anterior part of the cerebellar cortex was ablated.

Experiment 2.—*Small ablation of the cortex of the left cerebellar hemisphere; slight dysmetria; sacrifice one hundred and nine days after the primary procedure. S.P. No.* 21.

Operation. — The subject of the experiment was an immature female *Macaca mulatta.* On April 20, 1936, under sodium amytal anæsthesia the dura was opened, the occipital lobe elevated and the tentorium incised to the incisura. By blunt dissection a lesion 5 to 6 mm. in diameter and 3 to 4 mm. deep was made in the anterior portion of the left cerebellar cortex (fig. 2). There was but slight bleeding which was readily controlled. The occipital lobe was replaced, the dura tightly closed and the skin incision sutured with black silk.

Post-operative notes.—First day: The animal was quite lively and when placed in the corridor quickly ran from end to end. The stride was regular, but the left extremities showed high stepping. Occasionally the animal fell to the left side. There was no spontaneous tremor of any part of the body, and no tremor on volitional movement. It had no nystagmus.

Third day: The animal showed no abnormality of posture nor muscular tone. No motor weakness was apparent. The right upper extremity was preferred, but when the left was used there was little unsteadiness and no tremor. When the animal ran about in the corridor it deviated slightly to the right side. Both left limbs were slightly abducted. The hind limbs did not track well, but there was no constant deviation. There was still a slight hypermetria in the stride of the left fore limb. The cranial nerves functioned normally, and there was no nystagmus.

Fifth day: The animal fumbled a little when reaching for an object with the left upper extremity. There was no tremor. When running the left extremities were raised higher than the right, but the stride was even and regular and the animal did not fall. The animal jumped about, never missing its goal.

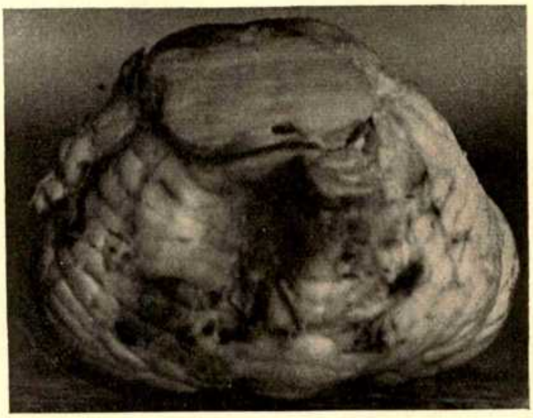

FIG. 2 (S.P. No. 21).—To show the ablation of the cerebellar cortex on the left side and the absence of injury to the cortex on the right side. (× 2.)

Eighth day: There was slight high stepping on the left side, and a week later this was barely noticeable. At that time the animal never ran into the wall, jumped accurately, and showed no ataxia in reaching for objects. Neurological examination was negative.

Second operation.—On the eighteenth day the right superior cerebellar peduncle was sectioned after removal of the right occipital lobe and the syndrome previously described was present and followed the usual course. On the sixty-fifth day the tip of the left temporal lobe was removed, and one hundred and nine days after the first operation the animal was sacrificed.

Pathological anatomy.—Gross examination showed a circular depression on the superior surface of the left cerebellar hemisphere reaching from the primary fissure to the anterior margin of the cerebellum and extending laterally from the vermis. A very superficial lesion was present on the anterior margin of the right cerebellar hemisphere. Serial sections of the pons, cerebellum and caudal part of the mesencephalon show that the cortex anterior to the primary fissure from the lateral margin of the vermis almost to the paraflocculus, has been ablated on the left side. The right superior cerebellar peduncle is completely sectioned just above the brain stem (figs. 2 and 3).

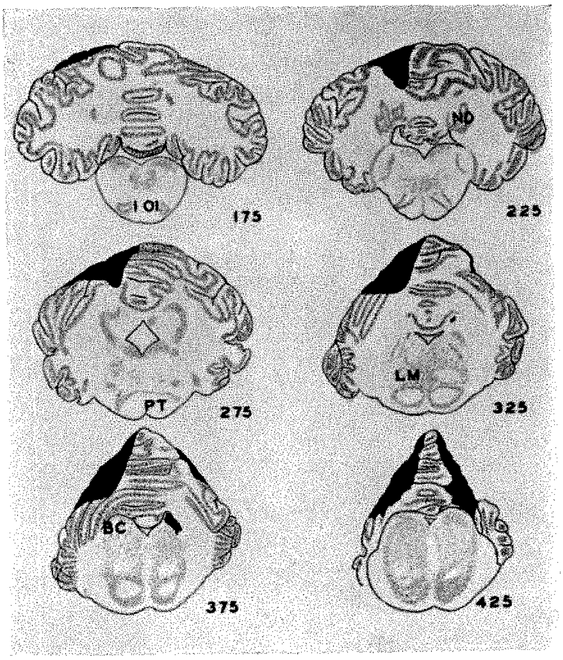

FIG. 3. Serial sections of the cerebellum of S.P. No. 21 (Case 2) to show the actual extent of the damage to the deeper structures of the cerebellum. The lesions are in black. (The numbers refer to the number of the section from which the drawing was made.)

On the basis of these, which we believe are rigid controls, it is our contention that the signs of inco-ordinated motor activity following section of the superior cerebellar peduncle is not due to co-incidental damage of adjacent structures but largely to interruption of efferent pathways.

III.—The Syndrome following Section of Both Superior Cerebellar Peduncles.

(1) *Simultaneous Section.*

Simultaneous bilateral section of the superior cerebellar peduncles has been carried out in two animals. Following this procedure the animals were prostrated for several days and required tube feeding. Occasionally spontaneous tremors of the extremities were observed and although movements were minimal, all voluntary activity showed extreme ataxia, with marked tremor and dysmetria. Any attempt to lift the head resulted in extreme swaying of head and trunk. One animal was able to sit up after a week by steadying itself with a hand against the cage. The head was usually tilted to the side upon which the operation had been performed. There was marked nodding tremor of the head for several weeks. A horizontal nystagmus, and in one case a vertical nystagmus, persisted for a few days. The visual fields were full. There was no facial weakness. The tendon reflexes, sluggish at first, became active later and were equal on the two sides. Pin-prick seemed to be appreciated equally everywhere. During the first week slight weakness was present in the extremities contralateral to the operated side. There was no abnormality in the resistance to passive movement in any muscle group.

It was not until two or three weeks following operation that the animals were able to walk. At first the gait consisted of pulling the body forward by fore-limbs, the buttocks and the flexed hind-limbs scraping the floor. Later the hind-limbs were slightly extended so that the buttocks were just raised from the floor. The trunk was not carried upon all four limbs for six to seven weeks following operation. In the early stages of recovery, in spite of the low centre of gravity, the animals swayed and fell from side to side. When the hind-limbs began to participate in the stride, marked irregularity of the force of the movements was evident, throwing the animal to one side and often precipitating a fall. Errors of range and rate of movement were also present. The kinetic tremor of the extremities became less marked in the course of a few weeks, but was present and definite as long as the animals were observed (in one case four months). After the first two months following operation there was little change in the syndrome; the ataxia improved very slowly.

Experiment 3.—*Section of both superior cerebellar peduncles; severe lasting ataxia of all four extremities; removal of cerebellum eighty-six days after the primary operation; slight exaggeration of symptoms* (*S.P. No. 14*).

Operation.—The subject of this experiment was an immature macaque. On February 10, 1936, under sodium amytal anæsthesia the left occipital lobe was elevated and the anterior portion of the cerebellum retracted; both superior cerebellar peduncles were then sectioned with a sharp iridectomy knife. The dura was firmly closed, the bone flap was replaced, and the skin sutured.

Post-operative notes.—On the first day the animal's general condition was good, but it was prostrated and lay prone on the floor with the head turned to the right. Occasionally there were spontaneous tremors of the left leg involving mainly the flexors and extensors of the hip. The animal preferred to use the left limbs, but the right limbs were moved about slightly. Movements of the extremities were through a small range and complicated by a severe, discursive oscillating tremor. Visual fields were full to gross tests. There did not appear to be any limitation of external ocular movements, but vertical nystagmus, with the quick component upward, was present. Occasionally horizontal nystagmus appeared on looking to the left with a counterclockwise rotatory component. The tendon reflexes were moderately active and equal on the two sides. There was no difference in the resistance to passive movement of the extremities right or left; it was neither increased nor decreased.

Third day: The animal was still prostrated and moved around but little. It was unable to sit up or walk. When its head was raised a pronounced side to side tremor developed; even when lying quietly there was occasionally a tremor of the whole body. Volitional movement of the extremities were so ataxic that the animal fed by bringing its mouth to the food. The extremities were moved but seldom, the right less than the left. The tendon reflexes were sluggish on the two sides but of the same quality. There was no abnormality in the resistance to passive movement on the two sides. The limbs were not "hypotonic."

Seventh day: The animal continued to lie on its abdomen, although it was able to sit up by supporting itself against the side of the cage. At rest in the prone position there was no spontaneous tremor of the body. When the animal raised its head a nodding tremor developed, and when squatting a tremor of the right upper and lower extremity (mainly abduction and adduction of the thigh) was occasionally seen. There was no hemianopsia. External movements were quite full and there was no nystagmus on looking in any direction. The animal still preferred the left limbs to the right, but there was no abnormality in the reflex muscular state on either side.

Thirteenth day: The animal lay prone much of the time, but now pulled itself forward by the fore-limbs. It was unable to stand unsupported, but by leaning against the side of the cage it could maintain a squatting position, occasionally falling to the unsupported side. Voluntary movements of the extremities were markedly ataxic, and tremor of such severity occurred that the animal was frequently unable to pick up a desired object. There was no longer any nystagmus. The reflex muscular status continued to be normal.

Twenty-sixth day: Usually the animal was seen sitting against the side of the cage with the head tilted to the right. There were no tremors of the body or limbs at rest. Both hands were used in picking up food, exhibiting a violent tremor which frequently dislodged the morsel from the hand. There was still a preference for the left hand. The animal was now able to walk cautiously. It barely raised the buttocks from the floor, projected the fore-limb (usually the left) forward, often with so much force that the animal fell to that side. If the latter did not occur, the right fore-limb was awkwardly thrown out and the himb-limbs shuffled forward. By this means, with frequent falls, the animal was able to move twenty feet in four or five minutes.

The cranial nerves presented no abnormalities except a slight right lower facial weakness. There seemed to be a slight weakness of the right extremities and the tendon reflexes on that side were more active than those on the left. There was slightly increased resistance to passive movement in both flexors and extensors of the elbow and knee on the right side. The pilomotor response was the same on the two sides.

Thirty-second day: The animal's general condition continued to improve. It sat or squatted against the cage wall with no tremor at rest. When standing without support, a swaying tremor of the body developed and the animal usually fell to the right side. The cranial nerves showed no abnormality except a slight right facial weakness. There was no evidence of increased or decreased resistance to passive movement in any group of muscles. The tendon reflexes were equal on the two sides.

Forty-eighth day: The animal was improving daily both in its general and neurological condition. It was now able to walk upright on all four limbs, but was extremely ataxic, falling to either side. The ataxia of the extremities was particularly pronounced when the animal reached for an object, a severe oscillating terminal tremor developing.

Fifty-seventh day: The animal was able to walk and run about, but still fell frequently owing to marked ataxia of the extremities. The reflex neuromuscular state remained normal.

At this time the upper portion of the premotor area of the right frontal lobe was removed. The animal had an uneventful convalescence, and the marked cerebellar syndrome continued without conspicuous alteration. For several weeks following this second operation a forced grasp could be obtained from the left upper extremity.

Eighty-sixth day: The animal still had a marked irregularity in the gait, swinging from side to side on a very wide base. When it reached for an object an oscillating tremor of the extremity became superimposed upon the jerkiness of the movement. When carrying food to the mouth a similar tremor developed with such severity that the morsel not infrequently was knocked from the animal's grasp.

Third operation. Decerebellation.—On the eighty-sixth post-operative day under sodium amytal anæsthesia a suboccipital craniectomy was performed, and after sectioning the inferior and middle cerebellar peduncles on both sides the entire cerebellum was removed.

Although completely prostrated for several days the animal was able to take food. Within a week it crawled about but could not squat without support. Volitional movements of the limbs were minimal and were accompanied by a tremor of about the same intensity as that before the third operation. A marked nystagmus was present, accentuated when the animal looked to the left. The animal's neurological state slowly improved, but even at the time of sacrifice, one hundred and sixty-two days after the primary operation, it was unable to walk without falling.

Pathological anatomy.—The cerebellum was placed in 95 per cent. alcohol, and after embedding in celloidin was cut serially at 25 μ and every twenty-fifth section stained with 0·1 per cent thionin. The dentate nucleus was then carefully studied microscopically. Almost all of its cells were shrunken and angular. The majority stained diffusely so that the nucleus could only be distinguished with difficulty. In other cells the nucleus was eccentric, and the cell cytoplasm diffusely and darkly stained. The dentate nuclei were not directly damaged by the primary operation. While the alterations in the constituent cells of the dentate nuclei are not the same as the retrograde cell changes seen in some other parts of the central nervous system such as the thalamus, the changes are sufficiently definite to state that the axones of almost all the cells of both dentate nuclei were interrupted; in other words, the section of the brachia conjunctiva was practically complete. Examination of the brain-stem of this animal at the time of sacrifice showed no gross damage to the mesencephalon in the region of the inferior colliculi.

(2) *Successive Section of the Superior Cerebellar Peduncles.*

Section of both superior cerebellar peduncles in two stages has been carried out in two animals. When so performed the operative procedures are not nearly so disturbing as simultaneous bilateral section. The clinical picture, once the acute stage has passed, is practically the same. For this reason no further description other than one protocol will be presented.

Experiment 1 (*continued*).—*Section of the left superior cerebellar peduncle: marked ataxia of the ipsilateral extremities gradually decreasing. Seventy-nine days later section of the right superior cerebellar peduncle; severe persisting ataxia with slow improvement. Sacrifice one hundred and fifty days after the primary operation; autopsy* (*S.P. No.* 15).

The effects of primary operation have been described in the first section of this paper. At the time of the second operation the animal's neurological status was almost stationary.

Second operation.—On May 1, 1936, under sodium amytal anæsthesia the right superior cerebellar peduncle was exposed and sectioned.

Post-operative notes.—Eight hours after operation the animal was reeling about, and on reaching the right upper extremity exhibited a marked oscillatory tremor through a range of 5 to 8 cm.; the left upper extremity was moderately ataxic—more so than previous to this second operation—but the ataxia was not nearly as severe as in the right upper limb.

First day: The animal had great difficulty in sitting upright and constantly clung to the side of the cage. When reaching for objects both upper extremities showed a severe oscillating tremor with dysmetria, but more pronounced on the right. When attempting to walk the animal literally fell all over itself and was unable to progress. External ocular movements were full and there was no nystagmus. No hemianopsia was demonstrable. Passive manipulation of the extremities showed little change in the resistance and no difference on the two sides.

Third day: The animal still clung to the cage. When placed on the floor it assumed a squatting position with a wide base and slightly asymmetrical postures of the extremities; the body swayed from side to side, and the animal staggered to the wall for support. The gait was irregular and disorderly. The limbs were flung about wildly as the animal leaped first to this side and then that, falling to right or left every few strides and crashing into any obstacles in its path. There was no apparent facial weakness but the buccal pouches were crammed full of food, possibly an indication of some difficulty in mastication. The animal vocalized loudly. No paralysis or paresis was apparent in any part of the body. The tendon reflexes were sluggish throughout, the left knee-jerk appearing slightly more active than the right. Both plantar reflexes were flexor. All four extremities were ataxic. The left limbs decomposed their movements in a jerky fashion with slight tremor; the right ones exhibited wide oscillatory tremors, particularly pronounced as the limb approached its goal.

Pin-prick seemed to be equally appreciated on the two sides. Placing and hopping reactions were active bilaterally. A slight paresis of piloerection on the left side was apparent when the animal became excited.

Fifth day: The swaying tremor of the trunk was no longer present, but the animal still maintained a squatting position with difficulty even on a wide base. The severe disturbances of the gait remained about the same. The ataxia of the extremities upon volitional movement was unchanged, the right exhibiting more tremor and unsteadiness than the left.

Eleventh day: In the cage the animal still clung to the wire for support. At times there was a slight nodding or side to side tremor of the head, and occasionally of the body. When forced to squat on the floor the limbs assumed a wide base, but even this did not prevent swaying and falling. It moved about by flinging the right upper extremity forward and projecting the body by contraction of the semi-flexed hind-limbs. This contraction was frequently of undue force, propelling the body abnormally high or laterally in the air and causing the animal to fling out the fore-limbs to break the fall. The right lower extremity sometimes failed to support the body at the proper time and the animal fell on the lateral aspect of the thigh. The walking posture was one of semi-extension of the fore-limbs and semi-flexion of the lower extremities so that the buttocks just scraped or cleared the floor.

The severe tremor of the right upper extremity upon volitional movement was less prominent than previously and there was little difference in the ataxia affecting the two upper extremities; both showed decomposition of movement, dysmetria, terminal tremor and fumbling. The resistance to passive manipulation was carefully examined but neither hyper- nor hypotonia could be detected. The reflex neuro-muscular state remained as previously.

Twenty-eighth day: The animal was able to climb about the cage without much difficulty although the body still swayed at times. The gait was so irregular that there was practically no stride, the animal staggering from one side to the other with occasional falls and high leaps into the air. At rest there was no tremor of the body or head. When reaching for an object with either upper extremity ataxia was quite pronounced; even when holding an object there was a slight tremor of the fingers and hands.

Fifty-sixth day: The animal was much steadier that at the earlier examinations, but still very awkward. The animal stood upon all four extremities when walking, and although frequently interrupted, progressive movements had a rhythm. The fore-limbs were usually widely abducted and the hind ones exhibited high stepping. Occasionally the movement of an extremity was with undue force throwing the animal to one side. The hind-limbs frequently struck each other or one of the fore-limbs, at times causing a fall.

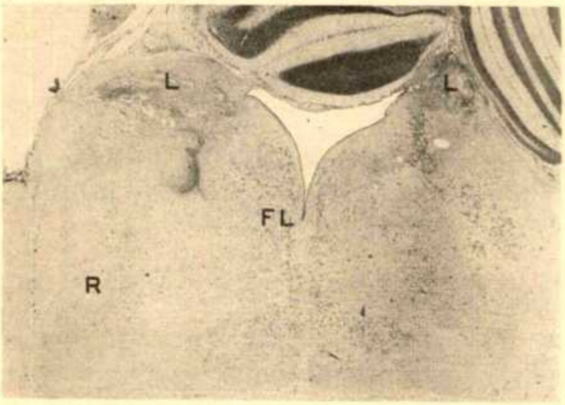

FIG. 4 (S.P. No. 15).—Photomicrograph to show the lesions in Experiment 1. (Nissl stain: × 12.)

Reaching for an object with either fore-limb exhibited decomposition of the movement, slight dysmetria and a terminal oscillating tremor through a small range. The ataxia of the upper extremities was about the same on the two sides. There was no abnormality in the reflexes.

Sixty-sixth day: When squatting the animal assumed a wide base, but the extremities maintained otherwise a normal posture. No spontaneous tremor of any part of the body occurred when the animal was quiet, but when excited a fine nodding tremor of the head was apparent. The gait was still quite irregular and on a wide base. The limbs were lifted too high and placed too wide. The stride was broken by the irregular force of the contractions of the extremities. The animal occasionally fell. Volitional movements of the upper extremities were performed with some decomposition into their constituent parts and showed slight dysmetria, terminal tremor manifesting itself most prominently by fumbling.

To confrontation tests the visual fields were normal, the pupils equal and reacting well to direct light. External ocular movements were full and there was no nystagmus. The tendon reflexes were moderately active throughout and equal on the two sides. There was no motor weakness. No abnormalities were detected in the resistance to passive movement of any part of the body. The placing and hopping reactions were active on both sides of the body.

At this time the right occipital lobe was ablated in order to facilitate stimulation of the cerebellar cortex at a later date. Five days later, seventy-one days after the secondary operation and one hundred and fifty days after the primary operation, the animal was sacrificed.

Pathological anatomy.—Gross examination of the specimen at autopsy showed a slight injury to the superficial cortex of the anterior margin of both cerebellar hemispheres. The pons, cerebellum and mesencephalon were embedded in celloidin, sectioned serially at 30 μ and every twenty-fifth section stained with thionin. An examination of these preparations showed that the superior cerebellar peduncle had been sectioned completely on the left side and except for the inferior hook similarly on the right side (fig. 4). The dentate nucleus was not damaged on either side, and the brain stem only slightly injured at the site of the section.

Discussion.

It is apparent that bilateral section of the superior cerebellar peduncles produces a severe and persisting inco-ordination of volitional movement. This disturbance is more than the arithmetic sum of the disability produced by two unilateral sections of the superior cerebellar peduncle. The gait is a striking example of this fact. Within a few weeks the animal with a unilateral section of the superior cerebellar peduncle is able to walk around without falling, whereas a monkey with both superior cerebellar peduncles cut staggers and falls even after four months. Moreover, certain features which are slight in the unilateral preparation become prominent when both superior cerebellar peduncles are sectioned. The tremor of the head and trunk is an illustration. In unilateral preparations a nodding tremor of the head is present at most for a few days, and in some cases may not occur at all. By contrast, the animal with both peduncles sectioned shows a severe tremor of the head and trunk during the acute stage of the syndrome, and after some months may exhibit the same tremor upon excitement or fatigue.

The accentuation of the ataxia of the contralateral limbs following section of the second superior cerebellar peduncle may be considered as merely the result of forcing the animal to use these extremities for more delicate movements, thus bringing out a disability which was concealed by the inactivity of the limbs. This is undoubtedly a factor, but we believe that it does not entirely explain the phenomena. The severity and duration of the disturbances in the bilateral as compared with the unilateral preparation, the accentuation of certain signs in the contralateral extremities following section of the second peduncle, all suggest that the superior cerebellar peduncle while mainly concerned in the co-ordination of ipsilateral muscular activity, has also a contralateral influence. It is the disturbance in gait and the tremor of the head and trunk which are most accentuated upon section of the second superior cerebellar peduncle. The bilaterality is apparent in the responses seen on electrical stimulation of the cerebellum (Magoun, Hare and Ranson [5]), and its anatomical basis has been shown by Probst [7], Marchi [6], and Walker [9].

It seems significant that certain signs of the syndrome are more readily compensated than others. The wide oscillating tremor of the extremities on volitional movement disappear in large part after a few weeks, while the decomposition of movement and dysmetria persist in some degree over a long period of time.

IV.—COMMENT ON THE SYNDROME OF THE SUPERIOR CEREBELLAR PEDUNCLE IN THE MONKEY.

The syndrome of the superior cerebellar peduncle, as we have described it, consists of phenomena of cerebellar disturbance, but certain signs found in man and generally considered as cerebellar in origin have not been present in the syndrome.

(1) *Nystagmus* is usually associated with cerebellar lesions, although many patients with cerebellar lesions do not exhibit it. This phenomenon was found only rarely in the above series and then as a transitory sign. Inability to obtain sufficient co-operation from a monkey to have the animal fix its gaze upon an object far to one side, the optimum position for bringing out nystagmus, may have concealed a mild degree of nystagmus in some of the above animals. However, in each instance the animal was carefully examined and although a normal range of eye movements was seen, no abnormalities were detected. It is possible perhaps that previous investigators [1, 2] who have described nystagmus as the result of lesions of the superior cerebellar peduncle may have damaged other structures in addition to the brachium conjunctivum.

(2) *Hypotonia.*—Decreased, but never pronounced, resistance to passive manipulation of the extremities have been encountered in this series. It has, therefore, been considered that, in the macaque monkey, section of the superior cerebellar peduncle does not produce significant hypotonia. Other investigators [1, 2] have reported such findings, but since they have also reported nystagmus in their cases, it may be that in the macaque monkey there may have been a common basis for both these phenomena in damage to the vestibular complex.

(3) *Spontaneous tremors, choreo-athetoid and rolling movements.*—Such abnormal motor phenomena as these have not been seen in any cases in the above series except in certain animals in which damage was done to the brain-stem at the time of operation and which died within a week afterward. Severe rolling movements and spontaneous tremors were present in these cases and were attributed to damage to the brain stem.

In the macaque monkey nystagmus, hypotonia and abnormal spontaneous movements should be regarded as due to other than direct uncomplicated section of the superior cerebellar peduncle. It is, of course, possible that these are the combined effect of section of the superior cerebellar peduncle and damage to the brain-stem, and that they may not occur with isolated lesions of either of these structures. This must be left for further experimentation. In higher primates and man such abnormalities apparently may be due to uncomplicated section of the brachium conjunctivum. In the chimpanzee, for example, cutting the superior cerebellar peduncle produces a marked hypotonia, and vascular lesions of the anterior superior cerebellar artery in man may cause hypotonia and nystagmus [8]. Such differences in the symptomatology of lesions of the superior cerebellar peduncle in the ascending phylogenetic scale point to a progressive development of the cerebellum both physiologically and anatomically.

Partial lesions of the superior cerebellar peduncle have been observed, but we have not seen selective involvement of the upper or lower extremity in any case. It is possible that if the lesion were appropriately placed such might occur, for there is some evidence of lamination within the superior cerebellar peduncle [2, 9]. Partial section of the peduncle has resulted in a mild syndrome which disappeared with slight residua within two weeks. In many cases the inferior hook of the brachium conjunctivum has been spared, for this lies within the brain-stem at the level of section. This did not appear to affect the clinical picture or the course of the syndrome.

SUMMARY.

(1) Unilateral section of the superior cerebellar peduncle in the macaque monkey causes a severe ataxia, including tremor, dysmetria and decomposition of movement in the ipsilateral extremities. The ataxia gradually diminishes but never completely disappears. The disturbance is particularly evident in the gait.

(2) Bilateral section of the superior cerebellar peduncles is followed by a similar but more severe and persistent ataxia involving all four extremities and to a lesser degree the trunk.

(3) Nystagmus and hypotonia are, if present at all, transient and insignificant.

(4) Partial section of the superior cerebellar peduncle causes a mild and rapidly subsiding syndrome.

It is a pleasure to acknowledge the kindness of Prof. John F. Fulton under whose supervision the above studies were made. His stimulating criticisms have been much appreciated.

The following abbreviations have been used in the illustrations: Aq. = Aqueductus Sylvii. B.C. = Brachium conjunctivum. F.L. = Fasciculus longitudinalis posterior. I Ol. = Nucleus olivaris inferior. L. = Lesion. L.M. = Lemniscus medialis. N.D. = Nucleus dentatus cerebelli. P.T. = Tractus pyramidalis. R. = Right side of the brain stem.

REFERENCES.

[1] FERRARO, A., and BARRERA, S. E. "The Effects of Lesions of the Superior Cerebellar Peduncle in the *Macacus rhesus* Monkey," *Bull. Neurol. Inst. New York*, 1936, 5, 165-179.

[2] FERRIER, D., and TURNER, W. A. "A Record of Experiments illustrative of the Symptomatology and Degeneration following Lesions of the Cerebellum and its Peduncles and Related Structures in Monkeys," *Phil. Trans. Roy. Soc. Lond.*, 1894, **B185**, 719-778.

[3] HOLMES, G. The Croonian Lectures on "The Clinical Symptoms of Cerebellar Disease and their Interpretation," *Lancet*, 1922, **1**, 1177-1182, 1231-1237 ; **2**, 59-65, 111-115.

[4] KELLER, A. D., and HARE, W. K. "The Rubrospinal Tracts in the Monkey," *Arch. Neurol. and Psych.*, 1934, **32**, 1253-1272.

[5] MAGOUN, H. W., HARE, W. H., and RANSON, S. W. "Electrical Stimulation of the Interior of the Cerebellum in the Monkey," *Amer. Journ. Physiol.*, 1935, **112**, 329-339.

[6] MARCHI, V. "Sull' origine e decorso dei peduncoli cerebellari e sui loro rapporti cogli altri centri nervosi," *Riv. Sperim. f. Fren. e. d. Med. Legal.*, 1891, **17**, 357-368.

[7] PROBST, M. "Zur Kenntnis des Bindearmes, der Haubenstrahlung und der Regio subthalamica," *Monatschr. f. Psychiat. u. Neurol.*, 1901, **10**, 288-309.

[8] RUSSELL, C. K. "The Syndrome of the Brachium Conjunctivum and the Tractus Spinothalamicus," *Arch. Neurol and Psych.*, 1931, **25**, 1003-1010.

[9] WALKER, A. E. "The Thalamus of the Chimpanzee." 1. Terminations of the Somatic Afferent Systems." *Journ. of Anat.* (to appear).

ATAXIA AND ASTEREOGNOSIS OF BULBAR ORIGIN.

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LESIONS of the medulla oblongata frequently produce a dissociation of sensation in which sensibility to pain and temperature are chiefly affected; this usually results from a lesion in the retro-olivary reticular substance, the vascular supply of which is derived from the posterior and inferior cerebellar arteries. Tactile and deep sensation are less frequently disturbed, in fact this type of dissociation can be produced only by a small lesion involving the arcuate fibres of the bulbo-thalamic tract which pass from the nuclei of Goll and Burdach to the piniform decussation, or by a lesion of these nuclei. In this case there is ataxia of movement owing to disturbance of deep sensation.

Ataxia resulting from disorders of sensation has been rarely observed in cases of tumours of the medulla or of the fourth ventricle, and only exceptionally in other affections. It has not been reproduced experimentally, but as a result of a small lesion of the nuclei of Goll and Burdach, in the course of the removal of a hæmangioblastoma of the medulla oblongata, we have been able to observe it in a pure state. This syndrome has certain features in common with tabes dorsalis, as the presence of ataxia and disorders of the deep sensibility, but it is distinguished by normal tendon reflexes.

Mme. C. Lea, aged 29, was sent to the Neuro-Surgical Clinic of Hôpital de la Pitié on January 17, 1936, by Dr. Bariéty, of Dr. Troisier's Clinic at Hôpital Beaujon, with symptoms of increased intracranial pressure.

She stated that since the beginning of 1935 she had lost several pounds in weight without any apparent cause; nevertheless, her health remained satisfactory and she could continue her occupations. In September, 1935, the loss of weight became more pronounced, and at the same time headache became a prominent symptom. The pain, localized in the occipital region, appeared most frequently in the morning on rising, and lasted the entire forenoon. It was not controlled by analgesics.

In the beginning of October, 1935, the headache became more intense and was accompanied by radiation of pain to the cervical and scapular regions. The patient repeated ceaselessly, "I have a pain extending from my neck to my shoulders," or else, "I have a torticollis, and I can't move." The pains seemed to be aggravated by food; they were continuous and made sleep impossible.

During the month of November she developed vomiting of the cerebral type in the morning before taking food, but also occasionally during the course of the day. At the same time disorders of equilibrium appeared: her gait became more and more hesitating and she felt herself drawn sometimes to the right side, but more often to the left. These symptoms were accompanied by dizziness in which the patient had the impression that everything was rotating around her. This gyratory sensation was accompanied at times by loss of consciousness lasting several minutes, and was followed by copious vomiting. In the beginning of December the patient was obliged to take to bed, as the inco-ordination and the vertigo rendered walking impossible, and ocular disturbances appeared.

On January 3, 1936, she was admitted to Dr. Troisier's Clinic, where papillœdema was noted. She was immediately sent to the Neuro-Surgical Clinic of La Pitié.

A neurological examination at La Pitié was entirely negative. The patient suffered, however, with violent headache and she vomited continuously, but consciousness was intact. There were no signs of inco-ordination or of ataxia, and all forms of sensation were normal. The reflexes were also normal and there were no meningeal symptoms. The functions of the cranial nerves were unaffected. There was no hiccough. Intelligence was well preserved.

A general examination revealed no disease. Her blood-pressure was 120/80; the Bordet-Wassermann reaction was negative; blood urea 40 mg. per 100 c.c.; lumbar puncture (performed in Dr. Troisier's Clinic) revealed albumin 1·21 grm., cellular elements 0·2 per c.mm.

Ocular examination. January 16, 1936 (Dr. Hartmann).—The left eye had been enucleated in 1924 after an accident while riding on horseback. In the right eye there was slight papillœdema; visual acuity was 5/7.50; the visual field, the motility of the eye and the pupil were normal.

Otological examination. January 17, 1936 (Dr. Winter).—Normal hearing on both sides. No tinnitus. There was marked vertigo with apparent rotation of external objects which coincided with the headache and the vomiting. No spontaneous vestibular symptoms were observed, but Bárány's test produced intense nystagmus on both sides, with inclination of the entire body and vertigo, indicating over-excitability of both labyrinths.

X-ray examination.—Apart from slight separation of the fronto-parietal sutures, no abnormal findings were visible in the stereoscopic films. The sella turcica, in particular, was of normal contour and dimension.

The history of the illness, the type of the headache and its characteristic radiation to the neck and shoulders, the presence of vertigo and of disturbances of equilibrium favoured the diagnosis of neoplasm of the posterior fossa. Nevertheless, in view of the absence of any objective cerebellar symptoms a ventriculographic exploration was made the morning of the operation.

Ventriculography.—Bilateral occipital puncture. The two posterior horns were dilated but not displaced, and the fluid was not under increased pressure. 85 c.c. of air were injected on the right side after removal of 60 c.c. of fluid. The ventriculograms revealed symmetrical dilatation of both lateral ventricles, which were neither deformed nor deviated; the third ventricle, which was dilated, had normal contours. The aqueduct was visible, but no air entered the 4th ventricle.

The ventriculogram, therefore, confirmed the diagnosis of a neoplasm of the posterior fossa.

Operation. (Drs. M. David and H. Askenasy.)—Horizontal position and local anæsthesia. The usual occipital approach was made for exploration of the posterior fossa. The posterior arch of the atlas was removed. The dura-mater of the cerebellar fossa was much more tense on the left side than on the right. A tumour seemed to be visible in the lower part of the cerebellum. A puncture of the left lobe through the dura-mater resulted in escape of 45 c.c. of a yellowish fluid which coagulated spontaneously. The dura-mater then collapsed and was easily incised. There was a bilateral pressure cone, more marked on the left side. The left cerebellar lobe had a yellowish colour at its inferior aspect; its lamellæ were distended, especially at the lower portion. An orange coloured mass about the size of a small date protruded from it. It was surrounded by numerous blood-vessels and appeared to be very vascular. After transverse incision of the left lobe of the cerebellum, it was evident that this mass represented a tumour in the wall of the cyst. The mural tumour and the membrane of the cyst were removed in one piece. The 4th ventricle was then explored. On separating the tonsils, another tumour similar to the preceding was discovered; it occupied the middle line and was inserted on the posterior aspect of the medulla oblongata about 8 mm. below the point of the calamus scriptorius. It had elevated during its development several of the numerous blood vessels surrounding it.

With the aid of electrocoagulation, utilizing a very feeble current, the tumour was gradually encircled; the blood vessels which surrounded it and fixed it firmly to the medulla oblongata were coagulated, and the neoplasm was removed in one piece. Its size was that of a hazel-nut. During removal of the tumour, which lasted over half an hour, no disturbance of respiration nor any marked modification of the pulse was observed, but on several occasions the patient hiccoughed and complained of intense pains in all four extremities.

A third but much smaller tumour was discovered on the lateral aspect of the medulla oblongata at its junction with the spinal cord. This mass appeared to be an agglomeration of numerous vascular bundles rather than a true neoplasm, and so it was judged useless to attempt its removal. After hæmostasis and verification of the permeability of the 4th ventricle, the dura-mater was partially sutured, the bone flap was replaced and the wound was closed by muscular and cutaneous sutures.

Post-operative course.—The patient returned to bed in a satisfactory condition. Respiration remained regular, although slightly accelerated; the temperature oscillated around 98·6° F. Deglutition was undisturbed, but she had occasional spasms of hiccoughing.

On the second day, the patient complained of an intense sensation of formication all over the body, and of inability to localise the position of her limbs. There was no paralysis, but marked disturbance of stereognosis and of the sense of position. The responses to the cerebellar tests were poor on both sides. Twelve days after the operation, the patient complained of a sensation of intense coldness in the right hand and foot.

During the month of February, when the patient began to move about, it was found that she was unable to stand or walk unless supported by the shoulders. She threw her legs forward precipitately in attempting to walk.

On examination a definite muscular hypotonia in the lower extremities was noted; the heels could be easily brought in contact with the buttocks. The tendon reflexes were normal. The cutaneous plantar reflex was flexor in type on both sides. The heel-knee test revealed a severe degree of inco-ordination on the right as well as on the left side; her movements were hesitant and she could not touch the patella even under visual control. She was incapable of following the tibial crest with the heel of the opposite foot. There was also a complete loss of the sense of position; the patient could not localize the position of her toes or of her foot; she could not tell whether or not her knee was flexed; on the right side she could not even say if her hip was flexed. She complained spontaneously that she "lost her legs in the bed." In the upper extremities, she did not recognize the position in which her fingers were placed, but sensation to heat, cold and pain was conserved.

During the month of March there was no adiadokokinesis, the ataxia diminished and the patient succeeded in walking, though very unsteadily.

Examination on April 20, 1936.—The patient walked with difficulty, holding on to the bed. She walked on her heels. While standing she managed to keep herself erect and to correct the tendency towards falling backwards, but when her eyes were closed she immediately fell backwards.

There was a certain degree of contracture in the lower extremities, especially on the left side. This could be overcome when the attention of the patient was distracted. The reflexes were normal and the cutaneous plantar reflex was flexor on both sides. The knee-heel test was ataxic. She could not recognize the positions of the toes and of the knee on either side. The patient had regained the sense of position in the fingers, except in the third and fourth fingers of the right hand. The examination of the cranial nerves revealed nothing worthy of note.

At present (June, 1936) the patient walks correctly on level ground, but still has difficulty in climbing stairs, especially in the dark.

It is interesting that from April 15 to 20 the patient complained of girdle pains around the lower part of the right side of her chest, associated with continuous vomiting and marked asthenia. There were no local or meningeal symptoms.

Pathological examination (Dr. Berdet).—The neoplastic tissue was composed of blood-vessels and connective tissue cells. The vessels were capillaries with extremely thin walls, formed by an endothelium with long and narrow nuclei. In a few of these capillaries the endothelial wall was surrounded by an external cellular lining containing nuclei which were round and more voluminous. The capillary network was markedly developed. The vessels were of varying calibre; in places they were very dilated, resembling those of splenic tissue. Here and there a few arterioles were present. We have not been able to demonstrate conclusively the presence of hæmatopoietic elements in the lumina of the vessels.

The intercapillary cells were large and generally round. Some were adherent to the vascular walls, but many had disappeared, leaving wide open spaces. Others appeared free in these spaces. The protoplasm of the cells was filled with lipoids and was vacuolated; their nuclei were pyknotic. Owing to poor fixation it was impossible to demonstrate conclusively the presence of a reticular network, but the lack of collagen in the capillary wall in sections treated by Mallory's stain, contrasted with the rich network obtained by the silver impregnation method, suggests that there existed an abundant reticular stroma.

The tumour was therefore a capillary hæmangioblastoma or an angioreticuloma, which had undergone xanthomatous degeneration.

Commentary.—There can be no doubt that the post-operative ataxia was not the result of damage of the left cerebellar lobe. In the first place there was no ataxia before operation in spite of the presence of a large cyst on the left side of the cerebellum. Secondly, it is well known that the removal of cystic tumours of the cerebellar hemispheres is generally followed by progressive and often rapid amelioration of the cerebellar disorders, and not by aggravation of these disorders. Lastly, the nature of the post-operative cerebellar lesion could not explain either the bilaterality of the ataxic troubles or the disturbances of the deep sensation.

The post-operative symptoms presented by our patient must have resulted from a lesion of the inferior part of the medulla oblongata, produced in the course of the removal of the bulbar angioma. This lesion can be delimited with considerable precision, as the area of insertion of the angioma was small and there was a minimum of local operative trauma. The tumour was inserted on the posterior aspect of the medulla oblongata, 8 mm. below the point of the calamus; it was symmetrically placed in relation to the mid-line, and within a circular area whose diameter was smaller than that of a fifty centimes piece.

A transverse section of the medulla oblongata at this level shows clearly (fig. 1) that the area of insertion of the tumour corresponded exactly to Goll's nuclei and to the internal portions of Burdach's columns where they enter their nuclei. It is probable, therefore, that an operative injury in this position was the source of the disturbances of sensation which produced the ataxic symptoms.

This syndrome is rare, but similar or related disturbances may be found in the literature. In most instances the lesions were tumours of the posterior fossa, particularly hæmangioblastomas. Cushing and Bailey [1] (obs. 19 and obs. 20) describe two patients with hæmangiomas in the region of the mid-line who presented, before operation, a definite unilateral astereognosis, for which reason operations were mistakenly performed on the parietal region. More recently, G. Roussy and G. Lévy [6] published a case of a tumour of the medulla oblongata of the polymorphous glioma type, in which there was a so-called cortical dissociation of sensation, and in particular astereognosis. This dissociation coincided with integrity of superficial sensation and very slight motor disturbances. The sensory disorders observed were of a pseudoradicular type, as they were in the right hand of our patient.

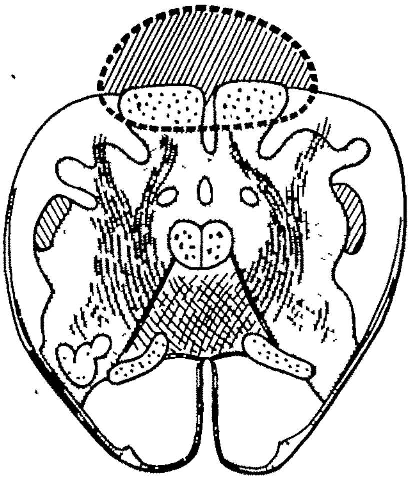

FIG. 1.—After Van Gehuchten. Transverse section of the medulla oblongata 1 cm. below the point of the calamus scriptorius. The area of insertion of the tumour corresponds to Goll's nucleus and to the internal portion of Burdach's column.

In a patient operated on by Clovis Vincent for an astrocytoma of the 4th ventricle, removal of the tumour was followed by a very marked hyperæsthesia to touch and to pain in the whole left lower limb and in the left half of the trunk up to the level of the xyphoid process, which disappeared in a few days. J. Lereboullet [5] and later Delay [2], in their thesis cite seven cases of tumours of the 4th ventricle, in which astereognosis was present. In most of these cases the tumour lay in the lower portion of the 4th ventricle and exerted pressure upon the lower segment of the medulla oblongata.

This type of sensory dissociation is even rarer in other lesions of the medulla oblongata. We have found in the French literature only two observations describing it. In both there was a pronounced ataxia, but the tendon reflexes were normal. André Thomas [7] has reported the history of a patient who, in addition to Jacksonian syndrome and a rotatory nystagmus, had loss of deep sensation on the right side, chiefly in the distal part of the upper limb, marked ataxia of the right arm, and disorders of temperature and sweating. The reflexes were normal. The nature of the lesion is unknown.

More recently, R. Froment and R. Masson [4] have recorded an absolutely identical case with pronounced disturbance of gait, which was aggravated by closing the eyes; marked inco-ordination of the right limbs and a severe degree of loss of deep sensation on the same side. The reflexes were normal.

The authors of these two observations assumed the existence of lesions of the spino-thalamic tracts in the medulla oblongata, probably in the internal arcuate fibres between the nuclei and the pinniform decussation.

The observation which we record here tends to confirm this hypothesis, as we have produced by a lesion of the nuclei of Goll and Burdach at the lower end of the medulla oblongata, a pure ataxia of the tabetic type, without disturbances of the tendon reflexes.

REFERENCES.

[1] Cushing, H., and Bailey, P. "Tumours arising from the Blood-vessels of the Brain.' Charles C. Thomas, Baltimore, 1928.

[2] Delay, J.-P. L. "Les Astéréognosies," *Thèse de Paris*, 1935.

[3] David, M., Thieffry, S., and Askenasy, H. "Angiome du bulbe coéxistant avec un angiome du cervelet. Ablation. Syndrôme d'ataxie postopératoire. Guérison," *Revue Neurologique*, 1936 (1), 975.

[4] Froment, R., and Masson, R. (Présenté par Garcin.) "Hémisyndrôme bulbaire 'direct' et séquelle d'angine diphtérique," *Bulletin Soc. Méd. Hôpitaux de Paris*, 1936, 571.

[5] Lereboullet, J. "Les tumeurs du quatrième ventricule," *Thèse de Paris*, 1932.

[6] Roussy, G., and Lévy, G. "Existence d'une association dite corticale des troubles de la sensibilité par atteinte bulbo-protubérantielle et médullaire supérieure," *Revue Neurologique*, 1930 (1), 145.

[7] Thomas, A. "Hémisyndrôme bulbaire inférieur direct," *ibid.*, 1914 (1), 468.

CEREBRAL INFECTION WITH *SCHISTOSOMA JAPONICUM*.

BY J. G. GREENFIELD AND BLAKE PRITCHARD.

THE following clinical and pathological data refer to two patients, each of whom presented a symptom complex suggesting the presence of a cerebral tumour, and in whom operation disclosed a mass in the brain identified as a collection of eggs of the *Schistosoma japonicum*.

CLINICAL DATA (B.P.)

Case 1.[1]—A lieutenant in the Royal Navy had the first of a series of epileptic attacks in December, 1935, at the age of 30. Four years earlier while stationed in Chinese waters he had often taken part in shooting expeditions in parts of the country in which the *S. japonicum* is known to exist. On these expeditions he had taken no particular precautions against infection by protecting his legs when wading through swampy ground. He had at that time an attack of diarrhœa lasting about three weeks without any recorded febrile disturbance and without any irritative skin rash. He had no reason for believing himself to be other than in perfectly good health when the epileptic seizures began: in particular he had had no headaches or visual disturbances. Neither he nor any relative is known to have suffered earlier from epileptic or from migrainous attacks.

The first attack occurred while at Gibraltar. He had refused an invitation to go ashore because he felt unwell and retired to his quarters. He was found unconscious, and on recovering had a slight headache. Five days later while resting in bed he became aware of a sensation, which he can only remember as unpleasant, in both legs and in the lower half of his abdomen. At the same time his heart palpitated and he noticed that his field of vision became obscured from the periphery up to the fixation point on the right side, with flashes of light in this non-seeing field. He then lost consciousness and recovered with a severe headache which lasted for two days. A few days later he had a third attack in which he did not lose consciousness and which was limited to the above visual phenomena without any headache, sickness or giddiness.

He was transferred to England, and on one further occasion had an epileptic seizure which he attributed to the abnormal position in which he had been kept while his skull was being X-rayed. In this attack there were exactly similar visual disturbances preceded by palpitations and paræsthesiæ of both legs and followed by a moderately severe headache: consciousness was lost on this occasion for ten minutes.

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[1] This is the case referred to by Edgar.

In addition to these spasmodic and transitory attacks certain persistent disturbances of behaviour began after the first and increased in severity after each of the later seizures. He had difficulty in finding suitable words during conversation, a disturbance which he described as a tendency to "stutter," although he had at no time any difficulty in enunciating correctly the words ready to his mind and had misplaced or misused words. He had also some difficulty in writing, which showed itself as a tendency to omit words, to reduplicate words or to repeat the individual syllables of a single word: he thought that some clumsiness in the use of his right hand, although not otherwise apparent to him, was partly responsible for this. He complained that his mental processes had become "slowed-up," e.g. he could not make the simplest arithmetical computation "in his head," but had to set it down on paper; even with this help he was quite unable, during the voyage home to England in January, to make the simplest calculation necessary to decide how long this journey would take and on what day he would arrive. As a navigation officer he had always had considerable ability in this way and was much perturbed by his mental dullness. On more than one occasion he had come into collision with the right-hand side of a doorway through which he was walking and he was in other ways also aware of some defect in his recognition of things seen and events happening in his right field of vision. Apart from those which immediately followed the seizures, he had had no headaches, but he had been aware since early in December that the left side of his scalp was sore when he brushed his hair. He had noticed no impairment of visual acuity with either eye and no vertigo. He said that in spite of the distress occasioned by his symptoms and of their threat to his profession, his sleep and his general health had remained good. He was eating well and his weight was stationary.

January 10, 1936.—On examination he was a thin but muscularly well-developed man, not presenting obvious evidence of ill-health or loss of flesh. His very light hair and facial pallor gave him a "bleached" appearance, but no undue pallor of his mucous membranes was detected. His emotional state was in every way normal, showing a degree of anxiety appropriate to his symptoms. He was alert and his co-operation was willing and excellent. His memory was unimpaired.

Speech: His conversation was fluent: hesitation before certain words was evident, but no omission or misplacement of words was noted and he named correctly—although in some instances after considerable delay—nearly all the common objects which were shown to him: he failed completely only in respect of a tape-measure which he described with periphrasis. His ability to understand what was said to him was invariably ready and accurate.

Writing: This was slow, but he wrote correctly several simple sentences from dictation. He said that the writing so produced was clumsy and ill formed in comparison with his habitual script.

Hearing. There was no defect by air or by bone conduction in either ear. Weber's test was not lateralized. There was no tinnitus.

Vision: V.A. Right eye $\frac{6}{6}$: left eye $\frac{6}{6}$. He noticed occasionally some temporary indistinctness of the test type, but could not further particularize with regard to this.

Visual fields: There was a right-sided homonymous defect at the periphery affecting the lower more than the upper quadrant. In addition there was an absolute, paracentral scotoma reaching to within 5 degrees of the fixation point and confined to the lower right quadrant in each eye (*vide* fig. 1).

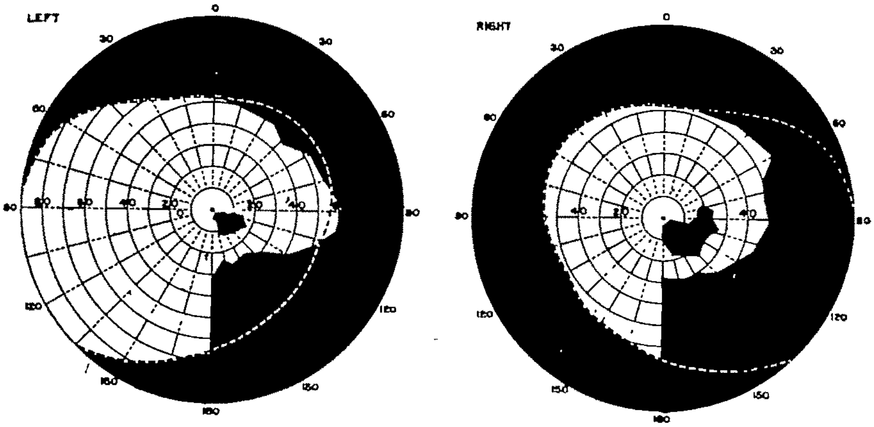


FIG. 1.—*Case* 1. Visual fields with 4 mm. white object in daylight.

Fundus oculi: In each eye the optic disc was unduly pink, the central pit was filled in and the veins thick: the disc edges were somewhat ill-defined, but no swelling was detected. The pupils were equal and normal in size and shape. They reacted briskly on illumination and on convergence. The external ocular movements were full in range and deviation was well sustained. The palpebral apertures were equal and normal.

On voluntary grimacing the left side of the face moved a little more promptly than did the right, but there was no other apparent asymmetry on movement or at rest, and blinking movements of the eyes were symmetrical. Movements of the jaw, palate and tongue revealed no weakness, and the sensitivity of the face and corneæ were normal.

There was no delay, weakness or clumsiness of the execution of voluntary movements with any limb and no alteration in the normal resistance to passive movement of the limbs. The tendon reflexes were brisk throughout and were symmetrical apart from a slight but significant exaggeration of the right knee and ankle jerks. The abdominal reflexes were brisk and equal in all four quadrants and the plantar reflexes were flexor. There was no impairment of sensibility, either superficial or deep, and in particular no defect in the cortical or discriminative aspect of cutaneous and deep sensibility. No irregularity of the scalp was noticed, but there was an area which was tender to firm pressure just to the left of the midline and vertically just behind the ear.

Examination of the cerebrospinal fluid by lumbar puncture gave the following results: Initial pressure 200 mm. of fluid with normal oscillations; protein, 0·22 per cent.; cells, 72 per c.mm., 93 per cent. lymphocytes; normal sugar and chlorides.

A radiogram of the skull revealed no bony abnormality. A ventriculogram (Mr. Julian Taylor) showed the following appearances: The right ventricle was normal, the left ventricle was narrowed and the body and posterior horn were displaced forwards; the left temporal horn was not filled. The 3rd ventricle was narrowed and displaced slightly to the right.

These clinical and radiological findings were interpreted as indicating the presence of a tumour in the left parieto-occipital area.

January 20. Operation (by Mr. Julian Taylor). The brain was decompressed over the supposed site of the tumour. The intracranial pressure was not noticeably increased. The superficial veins in the parieto-occipital region were dilated and the brain substance beneath them felt unusually firm. A friable, yellow tumour mass was removed from just beneath the surface of the brain.

On the day following the operation there was almost complete aphasia, considerable weakness of the face on the right side, gross weakness of the right arm with complete loss of all movement below the elbow and considerable weakness of the right leg. Sensory examination was not carried out.

Five days after the operation slow weak movements at the wrist and fingers had reappeared, and the leg had almost completely recovered. Sensory examination showed some impairment of recognition of touch and of the sense of position of the fingers in the right hand.

Histological examination (J. G. G.) of the mass removed at operation showed this to be a granuloma containing the eggs of *S. japonicum.*

Examination of the blood showed a mild secondary anæmia with some eosinophilia, that of the stools revealed the presence of a few spine-free ova resembling the eggs of *S. japonicum* and of the urine showed no abnormality (these examinations were carried out by Dr. S. R. Gloyne).

On the advice of Dr. Christopherson intravenous injections of antimony tartrate were given daily, from February 6 to March 6, using a total of 30 grains.

January 27: Clinical examination one week after operation; the patient is afebrile and the scalp wound healing satisfactorily. After two days of difficulty in urination, not however necessitating catheterization, normal micturition has been re-established. He is much worried by his aphasia; he does not misuse words, but conversation is often held up for want of some quite simple word. His understanding of spoken speech seems prompt and accurate. The right-sided hemianopia, complete when first tested three days after the operation, has now largely disappeared, but the loss, in the periphery in particular, is more extensive. There is definite weakness of the right side of the face, the right arm sways unsteadily when held extended and droops progressively if the eyes are shut. All movements of the limb are present but finger movements are still very clumsy.

In the right hand recognition of solid objects is faulty, but the loss not gross, i.e. he recognizes a tape-measure as not being the size of an orange and as being made of metal. Pin-prick is immediately recognized as are also cold objects. Light touches on the right hand are frequently missed. Localization of touches detected is moderately good; reference is usually peripheral when localization is defective. The sense of movement of the little finger is good; the sense of position of the little finger is very poor. Two-point discrimination is completely absent in the right hand. Vibration is readily recognized in the right hand. The right arm is a little spastic; the tendon reflexes are not noticeably increased. The abdominal responses are a little impaired on the right side. There is a slight clumsiness of independent toe movements of the right foot but no delay and no weakness of dorsiflexion of the ankle; there is brisk ankle clonus on the right and transitory knee clonus. The right plantar response is extensor. There is no impairment of pin-prick over the right foot and touches are readily recognized; there is no impairment of vibration sense. The sense of movement of the right great toe is delayed and the sense of position very poor. Two-point discrimination is very defective in the right foot.

April 28: He has been in Scotland and walking for up to two hours at a stretch. He feels restored completely to normal health, except for his mental ability; he is still very slow in arithmetical calculations. He notices no trace of speech difficulty. To-day he ran into a beacon standard on his right side. When adding several columns of figures he is apt to wander off into the wrong column. The scalp wound is well healed and the growth of hair excellent.

Motor, sensory and reflex examination of nervous functions yield completely normal results with the sole exception of a visual field defect. In the seeing parts of the right visual field there is grossly defective visual localization; all objects which he sees when presented in the right inferior quadrant he projects into the upper quadrant; the error in distance with an object 1 yard away is often 18 in.; objects seen in the right upper quadrant are falsely projected nearer to the mid-line, but only for about 6 in. at the same distance.

He fails in serial subtraction of 7 from 100 and in the addition and subtraction of more than two digits.

June 9: Feeling perfectly fit. Visual field defect and defective visual localization as before; serial subtraction of 7 from 100 accurate after two errors had been corrected by him. Addition and subtraction of two-figure numbers quite accurate.

August 22: Physical and mental testing gave completely normal results apart from the visual disturbance which is unchanged. Recently he has had three attacks of "dizziness" of instantaneous onset and of three minutes duration, associated with aphasia but with no headache or loss of consciousness.

June 15, 1937: He had one attack of the above kind which resulted in loss of consciousness for about half an hour. In all other respects he is well and the previous findings in his mental and physical state remain unaltered.

Case 2.—A lieutenant in the Royal Navy, aged 25. This patient was under the care of Dr. Gordon Holmes to whom we are indebted for the following notes :—

While playing cricket on July 4, 1930, he fell on the back of his head on baked mud ; there was no bump, pain, or after-effects, and he went on playing. Three days later he began to have severe headaches all over the head which continued for seven days. After freedom for three or four days the headache became much more severe. Since then he has been free for only a few days at a time. The headache was described as a throbbing headache all over the head, but worse in the left parietal region, and generally most severe on waking.

He had vomited a few times in the early morning during the previous few weeks. There was no vertigo, but a "tight" feeling in his head on standing up.

Since the onset of the headache he had noticed from time to time a bright yellow spot to the right and probably below the horizontal. This varied and sometimes persisted for two weeks. When the bright spot was present he found he could not see properly to the right. On examination on August 7, 1930, a right lower quadrantic hæmianopia was discovered.

For two or three weeks before this he found that he could not estimate the relative distances of objects from him ; he had difficulty in getting about, missed food on his plate, and in writing especially he got words wrong and his lines were oblique.

For five weeks he had made mistakes in dressing, placed arms in the wrong sleeves, tried to get the neck instead of the bottom of his shirt over his head, and put on his trousers back to front. He could not shave with the right hand.

For six weeks there had been dragging of the right leg in walking, and slight difficulty in movement of his right arm.

His speech was never affected, but for about two months he had been unable to read properly, as his eyes did not move correctly over the lines. He understood, however, everything which he wrote. In writing his right hand would not move correctly, and he frequently had to stop to think out some letters.

On August 7, 1930, a left subtemporal decompression was performed by Mr. McConnell, and four days later the left occipital lobe was explored, but nothing abnormal was found.

September 11, 1930 : Examination (by Dr. Gordon Holmes) : A tall, healthy man. Heart and thoracico-abdominal viscera normal. Trephine openings were present over the left occipital and the left lower parietal regions.

Visual acuity : $\frac{6}{6}$ right and left. Visual fields : loss in the lower parts of the right fields and considerable defect in their upper halves. There was evidence of slight disturbance of visual orientation. Intense papillœdema with hæmorrhages and exudates in both eyes was found. There was no nystagmus. The pupils were equal and reacted well. The motor and sensory functions of the 5th nerve were normal, and the corneal reflexes equal. Slight supranuclear palsy of the right lower face was found. The palate was elevated in the midline and the tongue was protruded straight.

No disturbance of articulation or aphasia could be made out.

Motor system: There was no wasting of muscles or change in their tone. The right arm was weaker than the left, and there was some inco-ordination of both right limbs of the sensory type.

Sensation: Touch and pin-prick were normally appreciated, but there was great loss of postural sensation in the right arm, less in the right leg. He did not recognize the form of objects in the right hand. The compass test showed a defect in the right hand.

Reflexes: The right arm-jerks were brisker than the left, the knee-jerks and ankle-jerks were equal, the right abdominal reflex was reduced, both plantar reflexes were flexor in type.

Mentally: He was bright and intelligent, and his memory and attention good. There was no evidence of apraxia.

September 15: Operation by Sir Percy Sargent. A large tumour was found and the greater part of it removed from the upper part of the left parieto-occipital region.

November 18: He was examined after being treated in the Hospital for Tropical Diseases by Dr. Hamilton Fairley, with tartar emetic. The right arm remained weak and the right leg was weaker than before operation, but both were improving.

The loss of vision in the right halves of both fields was greater than before operation. There had been no headaches, vomiting or vertigo. There was still a hernia and a discharge from the sinus over the operation wound.

On examination the papillœdema had almost subsided. There was complete right homonymous hemianopia. Speech was unaffected. Slight weakness of the right lower face was noted, and the tongue was protruded to the right.

The right arm was weak and there was still much loss of the sense of position and recognition of form in it.

The reflexes remained unchanged. The gait was almost normal, but he occasionally placed his right foot badly.

June 24, 1931: Slight discharge still came from the wound. He had no headaches and felt very well. He had been fishing and had walked up to four miles. The right hand was stronger, but he could not yet feel properly in it. The vision had improved. He read and wrote easily, but complained that his "speed of thought" was not as good as before operation.

On examination: The scalp was depressed over the wound. The optic discs were normal. There was still right homonymous hemianopia, but he had regained vision near the fixation points. His arms and legs were now equally strong, but there was some defect of the sense of position, of the recognition of form and of discrimination of compass points in his right hand.

He has not been seen since this date but he is now reported to be leading a normal life.

PATHOLOGY (J. G. G.)

The material received from the two cases was so similar that the same description, with minor variations, applies to both.

On *naked eye* examination it had the colour of brain tissue but was much firmer, and on the cut surface numerous small irregularly circular areas resembling minute abscesses with caseous contents were seen. The centres of these were of a cream colour which in fact did not differ much from that of the surrounding tissues. There was no brownish discoloration such as is found in infections with fluke worms of the genus *paragonimus*. The macroscopic resemblance to small tubercular lesions was thus very close. (Plate XII, fig. 1.)

On *microscopical* examination, however, an obvious difference was seen in that the centres of the foci stained fairly dark with hæmatoxylin, though very faintly with toluidin and methylene blue. This staining was due to the presence of numerous partially degenerated nuclei, many of which were pyknotic, and most of which stained to some extent with hæmatoxylin. Numerous ova were found among this degenerated material, both as collections of 10 or 20 towards the centre, and as isolated specimens near the edge. With hæmatoxylin and van Gieson staining in paraffin sections they were difficult to see, especially those in the centres of the foci, as the faint picric stain of the shell was lost among the darker staining of pyknotic nuclei. They show up better in sections stained with toluidin or methylene blue, which stained the shell faintly and the nuclei within it darkly, leaving the degenerated material round the ova unstained (fig. 2). In order to avoid fragmentation and undue shrinkage of the ova thick, frozen or celloidin sections were chiefly studied.

The ova were clearly those of *S. japonicum*. They measured in sections about 40 to 50 μ in width and 60 to 70 μ in length. The shell was thin, often bent or misshapen owing to artefact in cutting and mounting sections which were never thick enough to include a complete egg. In some of the most perfect specimens a small spicule or blunt process could be seen on the side of the egg midway between the centre and the anterior pole. The paired salivary glands were clearly seen near the anterior end in many ova and in most a variable number of germ cell nuclei were gathered in the centre or towards the posterior pole. In Case 1 a few of the ova which lay near the edge of a focus were surrounded by a narrow zone with a crenated outer margin which appeared to consist of granules and radially arranged spicules which had the same staining reactions as red blood corpuscles, but did not show the definite outline of these (fig. 3). It seemed likely, however, that they were derived from blood as the zone was only seen round ova which lay in the neighbourhood of small hæmorrhages.

Some ova near the edge of a focus were surrounded by a fairly wide zone of radially arranged fibroblasts and endothelial cells among which a few lymphocytes and histiocytes were present. There was no evidence of necrosis of tissue in this zone (fig. 5). A less regular zone of fibroblastic and endothelial cells bordered the caseous centre everywhere, separating it from the wall of collagen fibres and inflammatory cells which formed the outermost zone. In the fibroblastic layer a few multinucleated giant cells were seen in some of the foci. The nuclei were eccentric, and their shape oval or rounded, and on the whole rather more regular than that of tubercular giant cells which they otherwise resembled. Occasionally such a giant cell would be seen partially enveloping an ovum (fig. 6), but they often appeared to lie at some distance from any ovum. They may, of course, have been in contact with ova in a different plane, but as serial sections were not made this point could not be established.

This zone was usually rather sharply delimited by a wide irregular zone of collagen fibres which became progressively more infiltrated with lymphocytes and plasma cells as it was traced outwards. In some parts plasma cells were so numerous as to outnumber the lymphocytes, and everywhere they formed a large proportion of the whole. Polymorphonuclear and eosinophil cells were rare, although occasional examples were seen. This zone contained many small blood vessels and an occasional rounded mass of endothelial cells, similar to those seen in tubercle nodules (*see* fig. 5). It passed very gradually into more normal brain tissue, but for a considerable distance from any caseous focus, all the vessels were very heavily infiltrated with mononuclear cells. Here again the great majority of the cells were plasma cells, the remainder being lymphocytes and endothelial cells.

DISCUSSION.

In these two cases the mode of infection is fairly obvious. Wading in paddy fields in infected areas near the banks of rivers is the commonest means of infection, as the cercariæ, swimming in vast numbers near the surface of the water, become attached to the skin of the legs and gradually work their way through this into the blood-vessels of the legs. What is not so clear is the method whereby the ova reach the brain.

In most cases the adult worms lie *in copula* in the portal veins, and the ova are passed by the female, without leaving the male, into the smaller mesenteric venules. The parent worms have occasionally been found in the liver and the lung, and the discovery of ova, in parts of the body other than the alimentary canal and liver, has been attributed to embolism from the lungs (Faust). In the only reported case of infection of the brain with *S. japonicum* (Tsunoda and Shimamura) both the cortex, the meninges and the basal ganglia were involved, and it was assumed that the ova reached the brain by embolism. On the other hand in Müller and Stenders case of bilharzial infection of the lower part of the spinal cord, it was considered probable that the eggs were deposited in venules near the spinal cord, or were carried there from the veins surrounding the bladder.

In the present cases it appeared from the symptoms that cerebral lesions were limited to the posterior part of the parietal lobes and the occipital lobes. The eggs were present in fairly dense clusters in some of the foci, suggesting that they were deposited by the female either in or near the place where they were found. It is, of course, possible, although unlikely, that a very large number of eggs might be carried by the blood-stream to one part of the brain, but it seems more probable that the adult worms were lying in one of the cerebral venous sinuses, probably the lateral sinus. It would be an easy matter for the female to pass a certain distance up the posterior anastomotic vein from the lateral sinus, and to lay her eggs in the smaller venous radicles entering this vein. This assumption is in agreement with the clinical aspects of our cases and is not, according to Prof. Leiper (personal communication) at variance with the known habits of the parasite, which may be found in other veins than those of the portal system.

No recorded case of *S. japonicum* is known to have been contracted outside of the endemic areas in Japan, China, Formosa and the Philippines. In these countries the endemic areas of China are far the largest and most heavily infected. Most of the endemic areas lie in the Yangtze basin, and in them the incidence of this infection among the population averages 7 per cent. In some villages it is as high as 95 per cent.

Houghton's figures from Wuhu General Hospital show that of the patients in this hospital known to be infected, in 27 per cent. the disease is discovered by laboratory tests in patients admitted for clinical conditions not referable to schistosomiasis.

Since we have in the cases described evidence that this condition gives serious signs of cerebral disorder when it affects the brain, it is surprising that so far there exists on record only one other authenticated case of cerebral involvement.

This case, described by Tsunoda and Shimamura in 1906, was that of a native builder, aged 32, who had suffered from indigestion and abdominal pain in 1901. In 1903 he began to have convulsive seizures with loss of consciousness followed by aphasia: he also had severe headaches and became drowsy. On examination in November, 1903, after a series of right-sided Jacksonian convulsions which occurred at the rate of two or three each day, he developed a right hemiplegia. He died in August, 1904, and at post-mortem was found to have a diffuse thickening of the cerebral meninges with abnormal masses in the left parietal region, partly in the grey and partly in the white matter. He had also a large zone of softening involving the internal capsule, the optic thalamus and the basal ganglia on the left side. No abnormality was discovered in the right hemisphere.

Houghton refers without further data to one patient who had a partial hemiplegia and disturbance of speech with a blood eosinophil count of 47 per cent.

It is noteworthy that in the three cases in which the cause of the symptoms was verified at operation or at post-mortem, the earliest symptom of cerebral involvement was focal epileptic attacks, and in each case the masses were found on the left side of the brain. Thus the condition conforms with the generalization of Griesiger that parasitic infections of the brain show a strong liability to give rise to convulsive seizures. In two cases there was a history of transitory abdominal symptoms some years before the onset of cerebral symptoms. In both of the cases in which a granuloma was removed by operation and in which this was followed by the intravenous injections of antimony, the patients made an excellent symptomatic recovery.

CONCLUSIONS.

If a patient who is known to have sojourned in a part of the world infected with *S. japonicum* later develops focal epileptic attacks, the possibility should be considered that these may be due to a collection of the eggs of this parasite in the brain. Findings which would support this suggestion are a state of undernourishment with a mild secondary anæmia and a high eosinophil count in the blood and with a high protein and cellular content in the cerebrospinal fluid. Confirmatory evidence should be looked for in the stools where the ova were in both of these cases detected. The recorded cases, though only three in number, suggest that the left hemisphere may prove to be more liable to infection than the right. The prognosis with regard to survival and cessation of convulsive seizures is good when operative removal of the tumour is followed by a course of antimony tartrate.

SUMMARY.

(1) A description is given of the history, clinical condition, operation and subsequent progress of two patients suffering from infection of the brain with *S. japonicum*.

(2) In each case the most persistent symptom was a series of focal epileptic attacks.

(3) After operations, at which a mass of granulation tissue containing the eggs of the worm was removed, the patients were treated with antimony tartrate, and both made an excellent recovery.

(4) A description and a discussion of the pathological basis of the condition is given.

We should like to thank Professor R. T. Leiper for his help in diagnosis and his interest in these cases.

REFERENCES.

EDGAR, W. H. *Journ. Roy. Nav. Med. Corps*, 1936, **22**, 150.

FAUST, E. C., and MELENEY, H. E. "Studies on Schistosomiasis Japonica," *Amer. Journ. of Hygiene* (Monograph), 1924.

HENNEBERG, R. "Die tierischen Parasiten des Nervensystems." In Handbuch der Neurologie (BUMKE and FOERSTER), 1936, **14**, 286.

HOUGHTON, H. S. *Journ. Trop. Med. and Hygiene*, 1910, **13**, 185.

TSUNADA, T., and SHIMAMURA, S. *Wien. med. Wochenschr.*, 1906, **56**, 1682.

LEGENDS FOR PLATE XII.

FIG. 1.—*Case* 1. Low power view of lesion showing the grouping of small caseous foci surrounded by a zone of inflammatory cells and connective tissue. (Iron hæmatoxylin—van Gieson.)

FIG. 2.—*Case* 1. A group of ova in a caseous area. (Toluidin blue.)

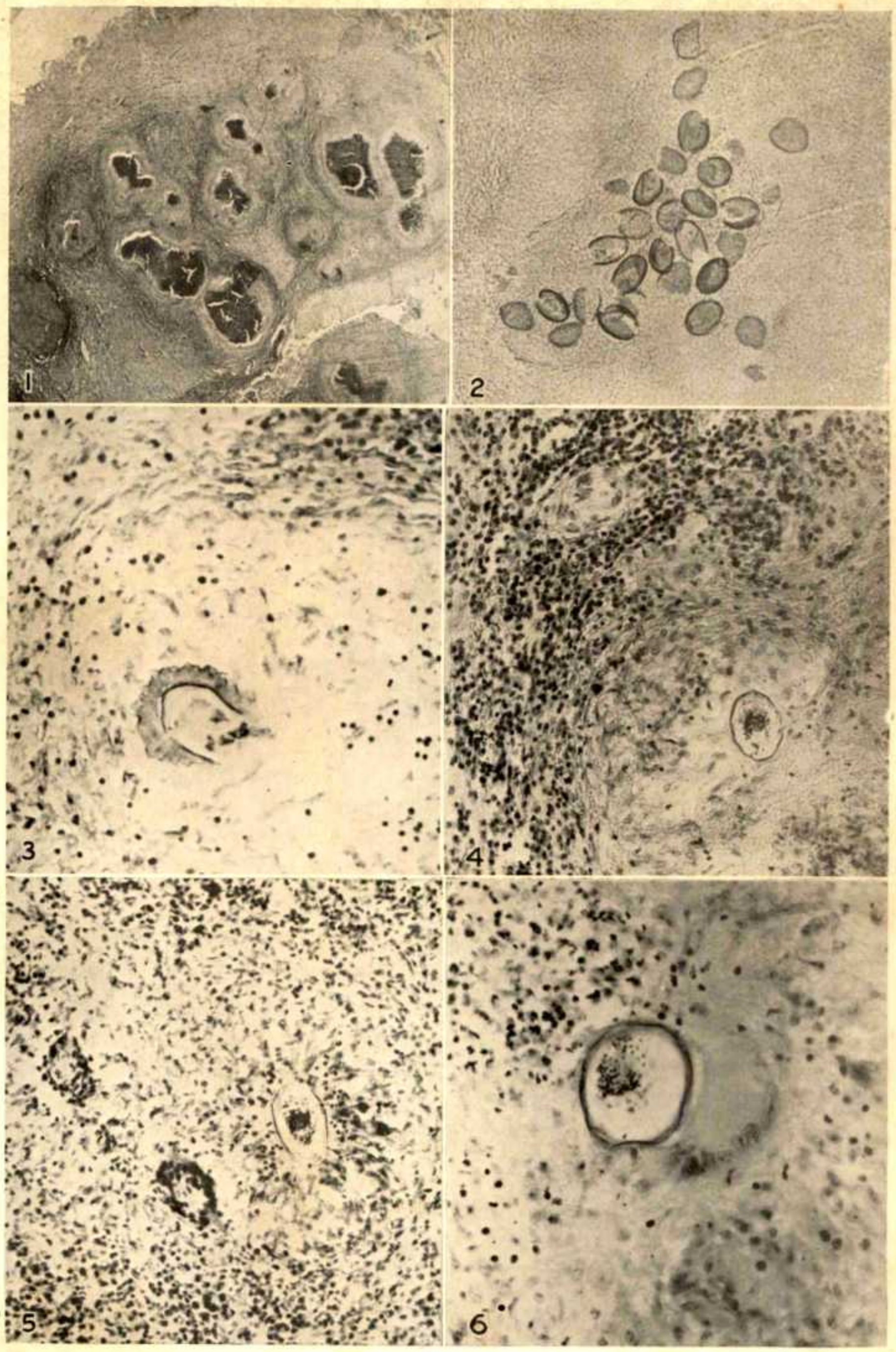
FIG. 3.—*Case* 1. An ovum in a small focus. The centre round the ovum is necrotic, and the ovum itself is surrounded by a belt of amorphous material. (Iron hæmatoxylin—van Gieson.)

FIG. 4.—*Case* 1. An ovum at the edge of a necrotic focus. Inflammatory cells, chiefly plasma cells, are seen on the edge of the focus; more centrally the tissue is semi-necrotic. (Iron hæmatoxylin—van Gieson.)

FIG. 5.—*Case* 2. An ovum on the edge of a necrotic focus surrounded by radially arranged fibroblasts. Two "foreign body" giant cells are seen near it. A rounded clump of endothelial cells is seen in the zone of inflammatory cells.

FIG. 6.—*Case* 2. An ovum on the edge of a necrotic focus partially enveloped by a foreign body giant cell. (Toluidin blue.)

PLATE XII



To illustrate article by J. G. Greenfield and Blake Pritchard.

NOTICES OF RECENT PUBLICATIONS.

The Diagnosis of Nervous Diseases. By J. PURVES-STEWART. London: E. Arnold and Co. 1937. Eighth Edition. Pp. 842. Price 35s.

In this new edition of his popular and useful textbook the author has added considerably to the text and in places has modified it, but its general plan remains unchanged; it is concerned mainly with the significance and interpretation of clinical observations, but the author also succeeds in presenting excellent descriptions and pictures of the commoner nervous diseases. The eighth edition should be as welcome to the student and practitioner as were its predecessors.

Pavlov and his School. By Y. P. FROLOV. London: Kegan Paul, Trench, Trübner and Co. 1937. Pp. 291. Price 12s. 6d.

This is an excellent account by one of his pupils of Pavlov's work, and particularly of his investigations by means of conditioned reflexes. The author presents clearly and concisely the gradual development of Pavlov's hypotheses and describes the more critical experiments on which they are based. His book will be therefore interesting and useful to those who have not read Pavlov's own writings, but are anxious to obtain a first-hand account of conditioned reflexes and the significance of the theories based on their study. The translation appears in excellent English.

The Normal Encephalogram. By L. M. DAVIDOFF and C. G. DYKE. London: Henry Kimpton. Pp. 224 with 149 Illustrations. Price 25s.

The experiences of the authors on which this book is based come from about 4,000 cases in which air was introduced into the cranial cavity by the lumbar or cisternal route. They emphasize the little risk attached to the procedure, but insist that ventriculography is the safer method where intracranial pressure is increased. They describe in the first place the normal ventricular system as it is made visible by encephalography, then the appearances of the cerebral gyri and sulci and of the subarachnoid cisterns, and finally indicate how various parts of the brain may be identified in the radiograms. The majority of the illustrations are reduced radiograms which are excellently reproduced. The volume will be a valuable addition to the neurologist's library.

Einführung in die Ventrikulographie. von B. SCHLESINGER. Berlin: Urban und Schwarzenberg. 1937. S. 246, mit 146 Abbildungen. Price RM. 18.

This book on the interpretation of ventriculograms in cases of cerebral tumour is distinguished by its wealth of illustrations and the fullness and clarity of the descriptive text. The majority of the figures are simplified line or stippled drawings of radiographs, but many of the latter to which he refers are reproduced. The author first describes the main anatomical features of the ventricles and other structures of the brain which can be demonstrated by injection of air into its cavities, then discusses the pathological factors which may deform the ventricles, and deals with the technique of the operation and the exposure of films. The complications and risks of the procedure are also discussed; his mortality did not exceed the low figure of 2½ per cent. The greater part of the volume is, however, devoted to the changes produced by tumours in various regions of the brain, which the author illustrates by cases collected from the literature as well as from his own practice. The book is an admirable contribution to an important subject and will prove invaluable to those engaged in it.

Lehrbuch der Geisteskrankheiten. VON O. BUMKE. München. J. F. Bergmann. 1936. 4te Aufl. S. 632. Price RM. 21.

In the seven years which have elapsed since the last edition of this important textbook appeared the outlook and trends of psychiatry have changed so much that the author has found it necessary to re-write a large number of the chapters, but its plan remains unaltered. The earlier chapters, which deal with causal factors and symptomatology, form an admirable introduction to the study of the psychoses, and the clinical descriptions and the discussions on diagnosis are clear and comprehensive. Considerable emphasis is laid on constitutional types and on the mental disturbances due to, or associated with, organic cerebral disease. The psychological analysis of disorders and symptoms is characterized by a scientific attitude which restrains the author from going beyond facts demonstrable by observation. His attitude remains antagonistic to the Freudian school, "Ich habe das alles immer für schrecklichen Unsinn gehalten."

Lehrbuch der Psychiatrie. VON E. Bleuler. Berlin: J. Springer. 1937. 6te Aufl. S. 496. Price RM. 18.

Very little change has been found to be necessary in the latest edition of Professor Bleuler's book which remains one of the most useful and reliable textbooks available for the student and practitioner; in fact it is so comprehensive that except for the specialist it will serve as a valuable work of reference. A new chapter by Professor Luxenburger on mental eugenics and hereditary factors in the psychoses is included. Due significance is given to the various types of pathological reactions in both the psychoses and psychoneuroses, and the psychological nature of the symptoms is fully discussed in these as well as in the other chapters. The sections on the legal aspects of mental disorders in Germany, Austria and Switzerland will be interesting and instructive to English readers.

Image de Soi. Par E. Tchehrazi. Paris: Librairie Le Francois. 1936. Pp. 106.

Under the stimulus of Professor Lhermitte, the author has undertaken a review of the significance in current psychopathology of the "body schema," to which Henry Head first drew attention. He is, however, much more indebted to Schilder than to Head. He examines in turn the clinical states, neurological and psychiatric, in which there is a disturbance of the appreciation of one's own body, and gives an unassuming interpretation, mostly in line with Schilder's, though much less influenced by psycho-analytic notions.

The Natural History of the Mind. By A. D. RITCHIE. London: Longmans, Green and Co. 1936. Pp. 280. Price 15s.

These Tarner lectures, in their revised form, seem to be addressed more to the academic psychologist and the philosopher than to the physician, who will probably find them barren. The discussion is mainly abstract, and much influenced by the ideas of Whitehead. The first three chapters cover the broadest biological questions; the next two are taken up with a rather elementary account of the functions of the nervous system, especially of the brain. The remaining three chapters include a cursory survey of what psychology sets out to study, an exposition of the author's views of sensation, perception and cognition, and a discussion of the problem of emotion and thought.

Conduct and Ability. By FRANCES BANKS. London: Methuen, 1936. Pp. 365. Price 10s. 6d.

Like most textbooks of psychology, this work puts emphasis on the views of one or two schools, while aiming at a presentation of the whole field. The writer succeeds in combining McDougall's hormic doctrine with Spearman's noegenetic theory, and in using this as the framework of a fair conspectus of psychology. The psychology of conduct and of knowing and learning are the main divisions under which the matter is expounded, an appreciable part of the book being given up to an account of methods and practical exercises.

Surprise and the Psychoanalyst: On the Conjecture and Comprehension of Unconscious Processes. By THEODOR REIK. London: Kegan Paul, Trench, Trübner and Co. 1936. Pp. 287. Price 12s. 6d.

Psychoanalysis is suffering from the qualities which have often seemed to be its strength. Its flexibility, its subtle theory, its apparent reliance on intuitive, rather than logical, interpretations, and its resistiveness to proof or disproof have led to schisms and uncertainties among its supporters, so that it is hard to discover where orthodox Freudian doctrine is now to be found. Dr. Reik joins issue with Fenichel and Reich concerning aspects of psychoanalytic method and psychology on which analysts were generally supposed to be agreed. Apart from these polemical sections he writes about his experience with the psychoanalytic procedure, and develops his views about the nature of comprehension, conjecture, observation and anticipation.

L'Astenia Psico-organica, nell'Indirizzo Individualistico. Del GIOVANNI CAPONE. Bologna: L. Cappelli. 1935. Pp. 204. Price L.32.

There is nothing original in this work, but it resumes in a systematic way the chief evidence for a relationship between neurotic and somatic anomalies, especially of the vegetative apparatus. The author has read widely; in his nosological conceptions he has been much influenced by the French school. Chapters on psycho-somatic correlations, heredity and constitution, personality, emotion and ætiology, lead up to detailed sections on the relation between the endocrines and psychological medicine generally, the autonomic syndromes and psychasthenia; psychotherapy also is briefly considered.

Infant Speech. By M. M. LEWIS. London: Kegan Paul, Trench, Trübner and Co. 1936. Pp. 335. Price 12s. 6d.

This contribution to the development of language during the first two years of life is welcome. The writer, who has the advantage of being equipped with a knowledge of phonetics as well as of educational psychology and the special literature of speech development, has observed carefully a particular child and attempted to relate his general behaviour to his behaviour as a speaker and listener. Unfortunately no systematic description is offered of the child's concurrent development and a consideration of the persistence of babble into the second year and its relationship to conceptual speech would also be of interest. The book is, however, carefully written and full of valuable observations and theoretical discussion. An exposition of the author's views on the nature of language introduces a section on the beginnings of utterance and response to speech; the fundamental processes of babbling and imitation are next considered. The acquisition of conventional speech and the approach to a conceptual use of words are the subject of the remaining two sections.

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EDITOR.

DECEMBER, 1937

BRAIN.

PART 4, VOL. 60.

EPILEPSY: A PAROXYSMAL CEREBRAL DYSRHYTHMIA.[1]

BY F. A. GIBBS, E. L. GIBBS AND W. G. LENNOX.

DISEASES change their names with increase, not of age (like Chinese children), but with increase of medical knowledge. Most disorders begin life bearing the name of the man who first recognized them or else they are temporarily tagged with some purely descriptive term. When the ætiology or pathology is discovered, the nomenclature is changed. Thus, *consumption* has become *tuberculosis*; *locomotor ataxia* has become *tabes dorsalis*; and *palpitation of the heart* has been classified into various disorders of cardiac rhythm as *paroxysmal tachycardia, auricular fibrillation*, &c.

However, some diseases never have outgrown their baby names. For example, ever since the days of Hippocrates, recurring and sudden loss of consciousness and of muscle control has been called "the falling sickness" or (in Greek) a seizure, "epilepsy." Thanks to the pioneer work of Berger in developing the electro-encephalograph, we can now make good the lack of thousands of years and adopt for this condition a name based on the underlying pathological physiology. We now know that epilepsy is due to the development of abnormal rhythms in the cerebral cortex; it is a *paroxysmal cerebral dysrhythmia.* This discovery places the study and understanding of epilepsy on a different and deeper level and requires a reorientation of our thinking.

We say "*a* dysrhythmia," because epilepsy is only one of many. For example, periodic breathing called "Cheyne-Stokes" respiration, is but the muscular registration of a medullary rhythm which is alternately slow and fast. Heart, viscera, endocrine glands, all have rhythms normal and abnormal.

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[1] From the Neurological Unit, Boston City Hospital and the Department of Neurology, Harvard Medical School, Boston, Massachusetts, U.S.A. This paper is No. XXV, in a series entitled "Studies in Epilepsy." Aid was received from the Josiah Macy, Jr. Foundation and from the Harvard Epilepsy Commission.

We have presented elsewhere details of observations [1, 2, 3, 4] and certain interpretations of results [5, 6]. At this time we shall review in brief outline seven new facts about epilepsy which we have gained in the last two and a half years by means of electro-encephalography. In this period we have made records of about 400 epileptic patients, examining many of them repeatedly. Of these patients, 120 had from one to hundreds of seizures while connected with the apparatus. With the exception of the pioneer observations of Berger, who published records of abnormal rhythm which occurred during seizures (fact one of our list), we believe the observations which we have presented, or now present, are new.

(1) *A seizure is accompanied by disturbance in the normal electrical activity of the brain.*—More exactly, a clinically observed seizure is but the outward manifestation of a disordered rhythm of brain potentials. We have many hundreds of records made during clinical *petit mal*, and dozens made during *grand mal* or psychic equivalents. In every instance the abnormal rhythm was unmistakable. However, several of the 120 patients who had seizures under observation showed no abnormality of rhythm during the seizure. We believe that in these instances the disordered rhythm involved a portion of the brain other than that from which we were recording. We have seen tremendous electrical disturbances in one area unaccompanied by disturbances in surrounding areas. We can record the activity of as many as six cortical areas simultaneously so that we probably do not miss abnormal cortical rhythms when these involve the outer surface of the frontal, parietal or occipital lobes. All parts of the cortex are not accessible from the surface of the head, however, and more important, disturbances confined to subcortical areas would not be recorded. Those few seizures which were not accompanied by abnormal cortical rhythms were bizarre in their patterns, falling in the group of "epileptic variants." For example, in one child the seizure consisted of gagging, profuse salivation, and slight muscular rigidity with only partial loss of consciousness, symptoms suggesting subcortical origin. In certain cases of hyperactive carotid sinus reflex, no obvious abnormalities appeared in the electro-encephalograph when the patient lost consciousness after pressure had been applied to the carotid sinus. We may conclude that in all but 2 or 3 per cent. of epileptic patients, electrodes applied to the

scalp transmit characteristic and unmistakable evidence of an epileptic seizure.

If a patient has a tonic-clonic convulsion during which he shows no abnormalities of cortical activity, he can be put down as either hysterical or a malingerer, for the disturbance in *grand mal* involves the entire cortex and is therefore readily detected with electrodes on any part of

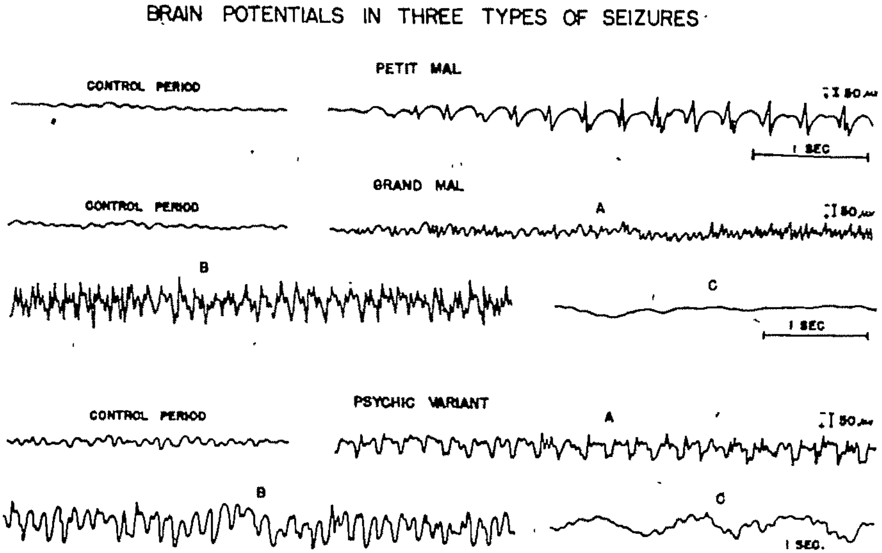

FIG. 1.—The wave formations which are characteristic of three types of epileptic seizures; *petit mal*, *grand mal*, and psychic variant. In each case the tracing under "control periods" was made in the normal period, before the seizure began. At the right is the signal made by 50 microvolts, and the space occupied by one second.

Petit mal.—The strip is the beginning of a *petit mal* record which lasted ten to fifteen seconds and then abruptly resumed the normal formation shown in the control period. The disturbance tends to have a slightly faster rhythm and smaller amplitude at the beginning. Between the start and the height of the seizure the rhythm may slow from 4 to 5 a second to 2 a second, and the voltage may increase from 50 to 500 microvolts. The *petit mal* formation is made up of two components, a wave with a duration of approximately one-third of a second, and a spike with a duration of one-tenth to one-twentieth of a second.

Grand mal.—The strip labelled A was made at the very onset of a *grand mal* seizure before clinical manifestations were present. There is an increase in the voltage of fast waves, those with frequencies around 20 per second. The strip marked B was made during the clonic phase of the fit. The fast waves are still present and still have an abnormally increased voltage, but they are now superimposed on slower waves which tend to be synchronous with the clonic jerks. The strip marked C was made during the post seizure stupor; all fast waves have disappeared and activity is confined to the frequencies of 2 to 3 a second. Voltage may be higher than in this record. As the patient regains consciousness, the normal rhythm gradually returns.

Psychic variant.—The strip labelled A was made at the beginning of the seizure. The patient stared, did not respond to questions, and when approached pushed the observer from him. The record is made up of square topped 4 per second waves on which are superimposed smaller waves, of a faster rhythm and a higher voltage than seen in the control period. Strip B was made later when the patient was talking volubly but incoherently. It shows almost nothing but high voltage, square or round topped 6 to 7 per second waves. During the taking of strip C the patient was quiet but still mentally confused. This portion of the record resembled that seen in alcoholic intoxication.

the head. The absence of electrical abnormalities does not permit a differential diagnosis between hysteria and certain bizarre forms of epilepsy. The presence of abnormalities of the electro-encephalogram may, however, demonstrate that certain cases of unexplained muscle jerkings, temper tantrums, or moments of abstraction are really minute *petit mal* or psychomotor seizures.

(2) *The three types of seizures have distinct cerebral rhythms.*—With the patient connected to the electro-encephalograph, the operator in another room can tell not only that the patient is having a seizure, but also the sort of seizure he is experiencing. The pattern traced by the electro-encephalograph can be clearly classified into three main groups which agree with the three main clinical types of seizures (fig. 1). In all types there is during the height of the seizure a great increase in voltage. The point which distinguishes the three is the difference in the frequency of the waves. The normal frequency of the brain potentials is around 8 to 20 a second. In *grand mal* these waves speed up to 25 to 30 a second, and appear in our records as sharp spikes. In psychomotor attacks (psychic variants) the rate slows to 3 or 4 a second with a square, flat-top wave predominant. In *petit mal* quick sharp spikes and slow, round waves at the rate of 3 a second alternate. We can say explicitly that in *grand mal* the cortical activity is abnormally fast; in a psychomotor attack, it is abnormally slow; and in *petit mal*, it alternates between fast and slow. The exact pattern of the seizure record tends to be individual for each patient and tends to repeat itself in successive seizures.

(3) *Regulation of cortical rate.*—The abnormal rhythms which we have described are clearly the cause of those symptoms (loss of consciousness and abnormal muscle movements) which constitute the seizures of epilepsy. Yet the more fundamental basis of the disorder is not the abnormal rhythm, but rather a defective control of rhythm.

Each cell may be considered as a rhythmically acting unit, like a muscle cell in the heart, which contains electro-chemical mechanisms which regulate the frequency and amplitude of the cardiac contractions. When cells become organized into tissues or organs, rate regulation is developed as a special function of a certain cell or cells. The vagus and sympathetic are rate regulators of the heart. The sleep centre is presumably a specialized nervous structure which helps to regulate cerebral rhythms. The activity of nervous tissue is of course related to physico-chemical changes in the body. In our opinion, in epilepsy certain of these rate-regulating mechanisms are defective. Normally the rhythm of the cortex is so well conditioned that there is only slight variation in frequency or in amplitude during the waking state.

As regards frequency regulation, the brain may be likened to a motor car which is being driven along a road with a ditch on the right called the *too slow* ditch and a ditch on the left called the *too fast* ditch. The rate-regulating mechanisms of the brain normally steer along the centre of this road, but when these mechanisms are out of order they steer the brain first to one side and then to the other. The more defective the

WAVE FORMATIONS OCCURRING IN PSYCHOMOTOR SEIZURES

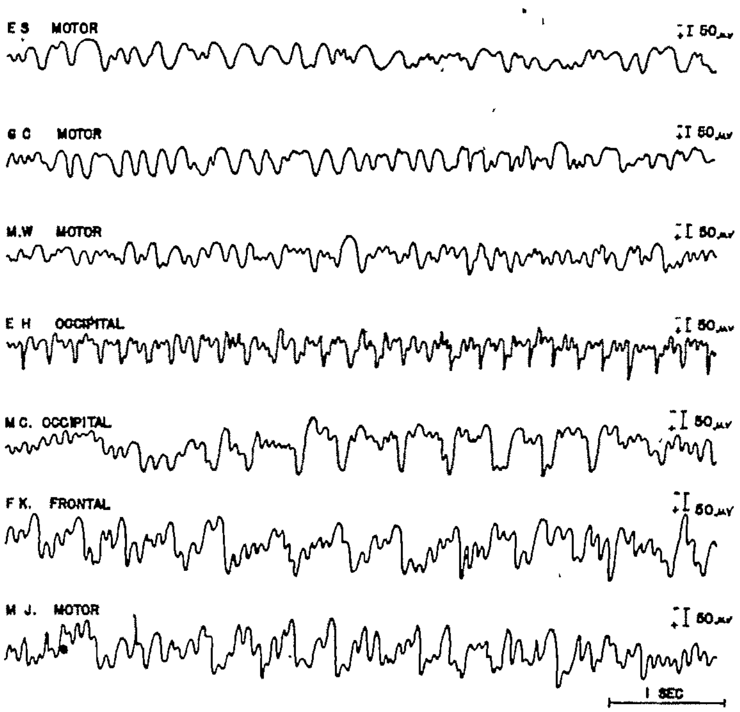

FIG. 2.—The electrical activity of the cortex during psychomotor seizures (7 cases). The distinguishing feature of these records is the presence of many high voltage rather square-shaped waves with a frequency of from 3 to 7 per second. The patient whose record is labelled E. S. had a seizure in which she cried, "I am having the heart scared out of me," and would let no one touch her. G. C. mumbled, flexed her arms and legs and attempted to get out of the chair. M. W. cried, "I can't stand it," and began to tear her clothes. E. H. grumbled about his boss, dropped his pipe from his mouth, lit a match and tried to pull the electrodes off his head. M. C. repeatedly said, "Where is my pocket book." F. K. mumbled incoherently, tore up a letter and tried to eat it. M. J. groaned repeatedly and tried to pull the electrodes off his head. In all seizures there was anxiety and negativism with appropriate but poorly co-ordinated movements.

steering (rate-regulating) mechanism the less quickly are deviations from normal corrected. *Petit mal* is an example of a minor disorder of rate-regulation in which the brain swerves quickly back and forth between too fast and too slow. In *grand mal* the rate regulators are so completely defective that the brain plunges far over to the too fast side, stays there for a considerable time, then goes over to the too slow side and remains there for a considerable time. In status epilepticus the brain goes through a number of these excursions to the fast side and then to the slow side before regaining its normal position with respect to frequency. In psychomotor epilepsy (psychic variants) the rate is abnormally slowed (fig. 2).

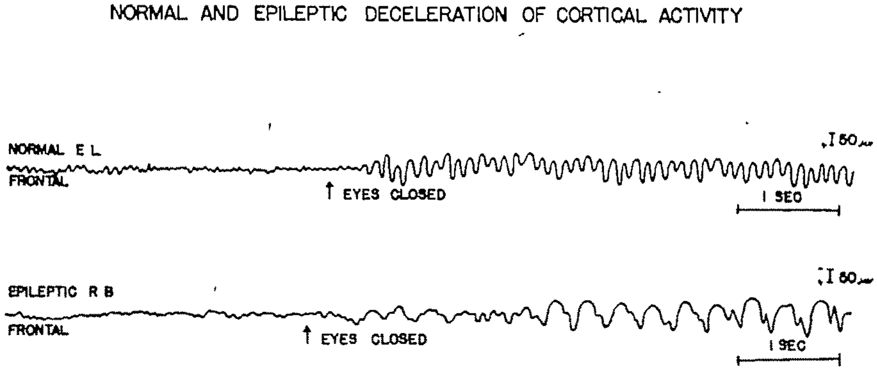

FIG. 3.—An example of the "overshooting" of electrical activity to which epileptics are liable.

In many normal subjects closing the eyes slows the cortical rhythms to approximately 10 per second, as is shown in the strip marked E. L.

The defect in rate regulation which is characteristic of epilepsy makes itself apparent in certain epileptics by extreme slowing of cortical rhythms when the eyes are closed. For example, R. B., a strip of whose record is shown in this figure, develops a steady 3 per second rhythm when the eyes are closed which soon shifts to a 3 a second wave and spike characteristic of *petit mal*. Such extreme slowing in a situation where slowing is normal is described as overshooting to the slow side. Overshooting to the fast side is also common.

Conditions such as excitement, closing of the eyes, or sleep, which modify the rate of the normal cortical rhythm, place a strain on the rate-regulating mechanisms of epileptics which they are frequently unable to meet (fig. 3). This we believe accounts for the tendency for seizures to occur on waking or on falling asleep. Seizures which follow emotional upsets (which cause moderate changes in rhythm even in normals) are often called "psychogenic." In general, electro-encephalograms made from time to time in epileptics show more variations than repeated electro-encephalograms of normal individuals.

(4) *Subclinical seizures.*—The electro-encephalogram often reveals

abnormalities of electrical activity which are not reflected in subjective or objective clinical manifestations. These abnormalities are of two types:—

First, the abnormal disturbance may be of the same pattern as found during clinical seizure, except much diminished in duration and in voltage. Subclinical *petit mal* attacks are more frequent than *grand mal.* They are seen usually in the records of patients with a history of very frequent *petit mal.* However, recorded *petit mal* lasting five, ten or fifteen seconds, may occur without clinical manifestations, and may be present in patients without a history of *petit mal.* For example, one of our patients a man, aged 26, had a head injury in football four years ago. A year later he had a generalized convulsion, and in the last three years has had a total of six or eight attacks of *grand mal.* He is employed in posting quotations in a stockbroker's office, a job which requires continued alertness. Under close questioning neither he nor his parents gave any history of *petit mal*; yet when the record was made he was having *petit mal* attacks at the rate of one every minute. He was able to repeat numbers and to recall whatever was said to him during the period of electrical commotion which was taking place in his brain. Yet, when we requested him to perform problems in arithmetic, or to write sentences necessitating thought, he would hesitate in his

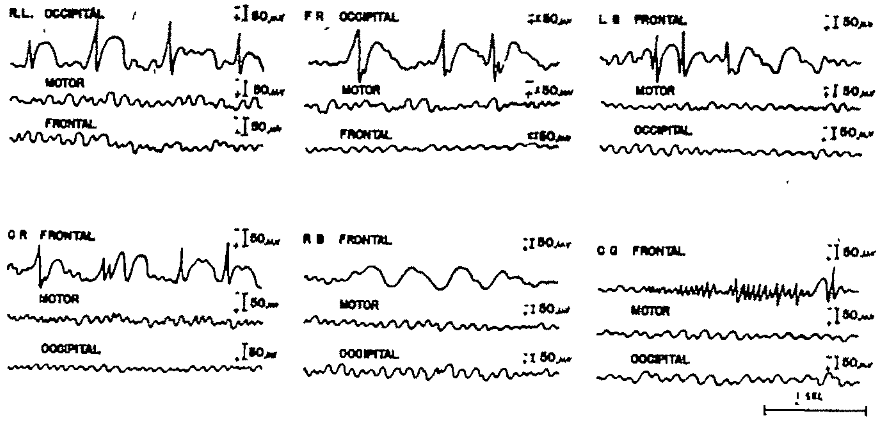
EXAMPLES OF LOCALIZED SUBCLINICAL DISORDERS OF CORTICAL RHYTHM

FIG. 4.—Six cases in which the electro-encephalogram gave evidence of a localized outburst of abnormal activity of the same type as was obtained from a wider cortical area at the time of a clinically obvious seizure. The localized disturbances shown here were unaccompanied by subjective or objective evidence of a seizure. The records marked R. L., F. R., L. G. and C. R., show activity of the *petit mal* formation. C. G. shows a crescendo burst of fast waves which are of the type seen in *grand mal*; following these there is a single *petit mal* formation.

writing or in his speech when the abnormal cerebral rhythm occurred. He was not aware of anything amiss, and when his hesitation was pointed out, considered it a natural pause. Undoubtedly, *petit mal* occurs much more frequently than is realized. Especially is this true of *petit mal* which occur during sleep. In sleep they are never recognized clinically, yet may come more frequently than when the patient is awake.

The second type of subclinical disturbance is the presence of isolated abnormal waves of large voltage, occurring singly or in a short series. These may have the form of single sharp spikes, a spike and rounded hump, or square or round topped slow waves. Each is a component of a pattern which is characteristic for one of the three types of seizures. A patient who exhibits one of these isolated abnormal waves oftentimes has a history of that form of seizure in which such waves are evident. Such isolated abnormal waves are oftentimes confined to one area of the cortex (fig. 4). These large voltage waves are not to be confused with the continuous slow frequency waves five to eight a second) found in all leads of many seriously deteriorated epileptics. Whether irregularly appearing slow, large voltage waves are peculiar to persons with epilepsy is a question not yet answered.

(5) *Prediction of a seizure.—Grand mal* and psychomotor attacks can often be seen on the record a short time before there is clinical manifestation of the seizure. We believe it probable that close analysis of a patient's record, with attention to the predominance of certain slow or fast waves, will give warning for many hours of approaching *grand mal.* In one patient, daily records were made for 195 days and most of the *grand mal* which occurred in that period were correctly predicted (fig. 5).

(6) *The point of origin of the abnormal rhythm.*—So far, most of our work has been done with electrodes placed at different points on the scalp, and we can speak with assurance only of what takes place over the various readily accessible areas of the cortex. Abnormal rhythms commonly appear first in the frontal area, but frequently they appear first in the parietal or occipital areas. In several instances, the right or left frontal "fired off" before other areas and in a number of these cases, there was a definite history of trauma to this portion of the brain. In many patients, however, the abnormal rhythm appears simultaneously in all leads.

In a number of instances, the abnormal waves of subclinical seizures were entirely confined to a certain area. In these instances, it seems that efforts at therapy might be directed at this particular spot. In one patient, we have made such a direct attack. This patient showed the wave and spike formation which is characteristic of *petit mal* only in the frontal areas, but each frontal lobe appeared to be independently affected. He had enostosis of the frontal bones by X-ray, and an atrophic appearance of both frontal lobes was found at operation. The anterior third of both frontal lobes was amputated by Dr. Jason Mixter. Since the operation, the abnormal wave and spike formations from the frontal

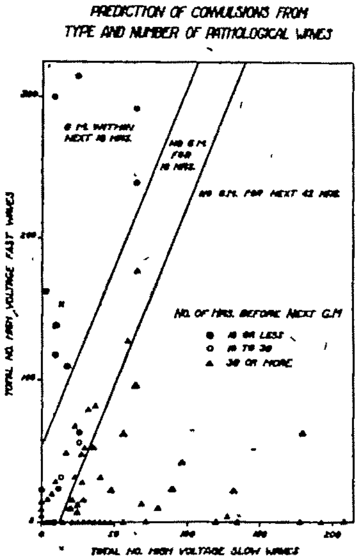

FIG. 5.—Prediction of convulsions from type and number of pathological waves in patient C. G., who has very frequent *petit mal* and occasional *grand mal*. Based on data obtained from analysis of a 15-minute record taken daily for 166 days, the abscissa represents the total number of high-voltage slow waves in the 15-minute record, and the ordinate the number of high voltage fast waves (spikes) in the same interval. Each symbol represents the record for a day. The symbol used varies with the number of hours after the record was made when the next *grand mal* occurred; a solid circle if less than eighteen hours, an open circle if from eighteen to thirty hours, and a triangle if more than thirty hours. The days in which the record was entirely normal are not charted. They were never followed by *grand mal*. If on a given day there were many high-voltage fast waves and few high-voltage slow waves, a *grand mal* seizure was imminent. If there were many high-voltage slow waves and a few high-voltage fast waves the patient was safe for a time. When there were few of both a seizure might be impending but was not imminent. The symbols represent what actually occurred, the diagonal ruling indicates the approximate prediction which could be made for the future. In the area marked *Grand Mal Within 18 Hrs.* there were three days on which a *grand mal* did not occur before eighteen hours had elapsed (two open circles and a square), on the day marked by the square. Double the usual dose of phenobarbitol had been given (for the effect of bromide in this case see fig. 6). In the area marked *No Grand Mal for 18 Hrs.* all predictions were correct; it contains only open circles and dots, the dots indicating that no seizure occurred for at least thirty hours. In the area marked *No Grand Mal for 48 Hrs.* records were characterized by very few high-voltage fast waves and numerous high-voltage slow waves. An actual record of this patient is shown in the frontal tracing of C. G., fig. 4. There are in this short space a dozen high-voltage fast (sharp) waves and one high-voltage slow wave.

areas (but not his normal cortical waves) have almost disappeared. *Grand mal* attacks have been reduced to a very small fraction of their former number and psychomotor outbursts, which were the most distressing aspect of the case, have ceased. In addition, the patient is more alert mentally than before his frontal lobes were removed.

(7) *Visualization of the effect of treatment.*—In the case of patients having very frequent abnormalities of rhythm, a few hours' observation will determine whether the condition is improved or made worse by a given drug or treatment. Thus, we find that *petit mal* rhythms may be precipitated by a short period of overventilation and may miraculously disappear while the patient is breathing air containing from 3 to 7 per cent of carbon dioxide. Abnormal rhythms are greatly increased by insulin and decreased by glucose.

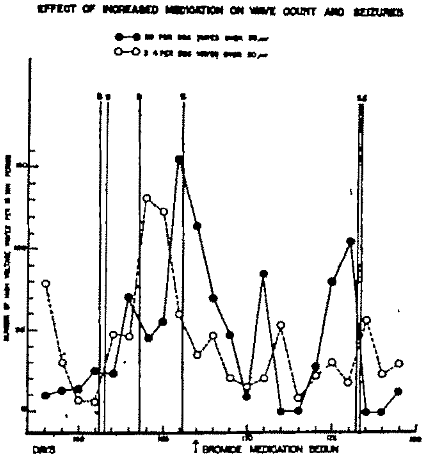

FIG. 6.—The effect of bromide medication on the incidence of seizures and on the number of high-voltage fast waves and high-voltage slow waves in a daily 15-minute record (Patient C. G.).

This is a continuation of the daily observations represented in fig. 5, except that the day-to-day changes can be followed by means of curves. The ordinate represents the number of high-voltage waves (either fast or slow) in the 15-minute record. The solid circles are the number of fast waves (20 per second) and the open circles the slow waves (3 to 4 per second). The perpendicular lines indicate the day and approximate hour when convulsion occurred. The patient had been taking daily small doses of phenolbarbital. After the 167th day she was given calcium bromide, 60 to 80 gr. daily. Experience based on the analysis of the previous 166 daily records of this patient indicated (*see* fig. 5) that when the number of fast waves greatly exceeded the number of slow waves the patient was due for a seizure within eighteen hours. However, on five of the days, after bromide medication was started the fast waves were much more numerous than the slow waves and yet no seizure resulted. It was only when the slow waves decreased in number and the fast waves rose to a peak that the situation got too much for the bromide to control and two seizures occurred.

Sedative drugs have a varying effect depending on the type of abnormal rhythm. The anti-epileptic drugs, phenobarbital and bromide, given in large doses intravenously while the record is being made cause a decrease in the rate of cerebral rhythms. These drugs are, therefore, valuable in conditions of abnormally fast rate, namely, *grand mal*; they may or may not favourably effect *petit mal*; and they actually accentuate the slow waves of a psychomotor disturbance. These laboratory observations are in agreement with our clinical observations. More than once we have unwittingly precipitated psychic episodes in patients subject to them by the intravenous injection of 10 gr. of phenobarbital sodium.

Although records of patients who are taking phenobarbital or bromide cannot be distinguished from the records of patients who are not, careful analysis of the record of a patient having frequent abnormalities will show the effect of the drug on his abnormal rhythm. If such a rhythm is a fully developed subclinical seizure, intravenous injections of bromide or of phenobarbital may inhibit or disorganize the rhythm. If there are isolated large spikes and large slow waves, the drugs may alter the ratio of their frequency.

The manner in which increased sedation effected the pathological activity of the cortex in one patient, who is subject to both *grand* and *petit mal*, is shown in fig. 6. In this patient a high ratio of large voltage fast to large voltage slow waves signalled an approaching *grand mal* seizure. When not taking bromides a convulsion was always followed by a sharp decrease of large voltage fast waves (spikes). The use of bromides seemed to raise the seizure threshold and did not permit so complete a discharge of *grand mal* activity, for when bromide was being given the fast waves decreased only slightly after a convulsion and then increased again rapidly so that the patient soon was having seizures as frequently as ever.

In addition to artificial means of inducing or of modifying the abnormal rhythms of epilepsy, we have observed that normal mental activity tends to inhibit, and unpleasant emotional states to augment, the frequency of *petit mal* rhythms. The clinical implications of these observations are obvious.

CONCLUSIONS.

The electro-encephalogram demonstrates the pathological physiology of epilepsy to be a paroxysmal cerebral dysrhythmia.

On the basis of some 900 hours of records obtained from a group of 400 epileptic patients, of whom 120 had from one to hundreds of seizures while the record was being made, we have secured the following data concerning epilepsy :—

(1) Seizures involving the cortex are accompanied by distinct and characteristic fluctuations in the action potentials of the brain.

(2) The rhythm which obtains during seizures is distinctive for the three main types: *grand mal* has a fast, psychomotor attacks (psychic variants) a slow, and *petit mal* an alternating fast and slow rhythm. The exact pattern of the seizure tends to be characteristic for each patient.

(3) Antecedent to these gross abnormalities of rhythm is the lack, in epileptics, of a competent control of cerebral rhythms.

(4) Some patients have subclinical seizures, which are typical short disturbances of rhythm not attended by subjective or objective evidence of a seizure. *Petit mal* may occur during sleep.

(5) There is evidence that *grand mal* may be predicted many hours in advance.

(6) In some patients abnormal activity begins in one area of the cortex and spreads to involve other areas. One patient with abnormal spikes confined to the frontal area has greatly improved following bilateral amputation of his frontal lobes.

(7) Electro-encephalography has been found useful in determining the value of various methods of therapy without having to wait for clinical seizures. Because anti-convulsant drugs slow cortical rhythms, they are more effective in *grand mal* than in other types of seizures. The inhalation of carbon dioxide and the administration of glucose are effective in temporarily abolishing certain abnormal rhythms. In some patients attention prevents the development of abnormal rhythms.

REFERENCES.

[1] GIBBS, F. A., DAVIS, H., and LENNOX, W. G. "The Electro-encephalogram in Epilepsy and in Conditions of Impaired Consciousness," *Arch. Neurol. and Psych.*, December, 1935, **34**, 1133.

[2] GIBBS, F. A., LENNOX, W. G., and GIBBS, E. L. "The Electro-encephalogram in Diagnosis and in Localization of Epileptic Seizures," *Ibid.*, December, 1936, **36**, 1225.

[3] LENNOX, W. G., GIBBS, F. A., and GIBBS, E. L. "Effect on the Electro-encephalogram of Drugs and Conditions which Influence Seizures," *Ibid.*, December, 1936, **36**, 1236.

[4] GIBBS, F. A., GIBBS, E. L., and LENNOX, W. G. "The Effect on the Human Electro-encephalogram of Certain Drugs which Influence Nervous Activity," *Arch. Int. Med.*, July, 1937, **60**, 154.

[5] GIBBS, F. A., GIBBS, E. L., and LENNOX, W. G. "The Various Cerebral Dysrhythmias of Epilepsy, and Measures for their Control," *Arch. Neurol. and Psych.* (In press.)

[6] GIBBS, F. A. "Interpretation of the Electro-encephalogram," *Journ. Psych.*, 1937, **4**, 365-382.

SOMATIC MOTOR AND SENSORY REPRESENTATION IN THE CEREBRAL CORTEX OF MAN AS STUDIED BY ELECTRICAL STIMULATION.[1]

BY WILDER PENFIELD AND EDWIN BOLDREY (MONTREAL).

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(1) INTRODUCTION.

RECENT experimental work on the localization of motor function in the cerebral cortex has spurred us to make a complete analysis of the records of our patients (163 in all) upon each of whom we have carried out electrical exploration of the cortex under local anæsthesia.

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[1] From the Montreal Neurological Institute and the Department of Neurology and Neurosurgery of McGill University, Montreal. Read before the American Neurological Association, Atlantic City, June 4, 1937.

This has led us to conclusions which differ somewhat from those published by other observers in regard to the localization both of sensory and motor function. Often we have found it impossible to confine functional representation within strict cytoarchitectural boundaries. The human cortex shows definite differences from that of other mammals and human pathological processes introduce important new elements.

(2) HISTORICAL NOTE.

Flourens (1842) carried out experimental removals of areas of brain and concluded that up to a point any part of the cerebral hemispheres could quite adequately exercise the function of the whole. This attitude, which bears some resemblance to that recently adopted by Lashley (1929) was considered to deny the possibility of circumscribed localization of function in the brain.

Broca (1861) gave the most effective impetus to the search for localization of function when he described an area of the left hemisphere of man as a specialized speech centre. Hughlings Jackson (1864) noted an association between speech defect and right sided chorea, saying that he saw "no more difficulty in supposing that there are certain convolutions superintending those delicate movements of the hands which are under the immediate control of the mind, than that there is one, as Broca suggests, for movements of the tongue in purely mental operations."

To Fritsch and Hitzig (1870) must be given credit for the first successful, controlled direct electrical stimulation of the mammalian cerebral cortex. By applying galvanic current through bipolar electrodes to the anterior half of the dog's hemisphere they obtained movements of muscle groups in the opposite half of the body. From the posterior part of the brain they secured no motor movements. Their map contains five motor points. Jackson was jubilant at this verification of his hypotheses and said (1873) the work of these experimenters demonstrated "that discharge of convolutions develops movements, notwithstanding that destruction of limited parts of the brain produces no obvious loss of movements."

Ferrier quickly took up the work in England and in 1876 published the results of repeated cortical stimulation in several species. Using a faradic current he obtained movement from points behind the Sylvian fissure, results which were roundly criticized by Hitzig. Nothnagel (1873), Hitzig (1874), Schiff (1875) and Hermann (1875) thought that the cortical centres were really sensory centres for "muscle sense," to use the words of the first two.

Dupuy (1873), Sanderson (1874) and Carville and Duret (1875) agreed that spread of current, principally to subcortical centres, accounted for the movements recorded. With this Ferrier (1876) could not agree, but he did admit that motor response might be an expression of sensation and that the character of the sensation might determine the nature of the movement. Although their work dealt chiefly with cortical removals, Luciani and Tamburini (1879) and Munk (1890) added confirmatory evidence to the sensorimotor conception of the Rolandic area.

In 1888 Dana reported 142 cases of sensory disturbance in man associated with cortical paresis. He observed that all cases of cortical anæsthesia were associated with some amount of paralysis.

Horsley and his collaborators conducted a minute examination of the motor area in apes. Beevor and Horsley's map of the cortex (1890) showed that there were motor points anterior and posterior to the Rolandic fissure, and overlapping of cortical areas. Bilateral innervation, they found, was confined to mouth and throat movements. In the higher apes they found inexcitable spaces among the normal areas of the pre-Rolandic cortex.

In 1894 Mott summarized the attitude of the three camps with divergent views on Rolandic cortex function. Ferrier, Schafer and Horsley believed the area to be purely motor. Schiff was certain it was purely sensory. Hitzig, Bastian, Bell, Wundt, Hughlings Jackson, Munk, Tripier, Luciani and Mott would call it sensorimotor. Sensory information in animals, of course, could be obtained only by extirpation experiments. Although it was not then clearly established, the idea of a sensorimotor cortex was generally held.

It was the work of Grünbaum and Sherrington (1901, 1903) which, according to Dusser de Barenne (1935), caused the change of opinion from the idea of sensorimotor cortex to the conception of a pre-Rolandic motor cortex separate from the sensory region. They worked with a unipolar electrode using weak currents to avoid seizures. The animals, however, were under general anæsthesia. In anthropoids, under those conditions, they found the excitable cortex to be limited to the precentral gyrus (fig. 1). This gyrus in anthropoids contains Areas 4 and 6.

In no case did they find primary motor response postcentral to the fissure of Rolando. They obtained discrete movements of ear, nostril, palate, lips, jaws, vocal cords, chest and abdominal wall, pelvic floor, anal and vaginal orifice as well as of the extremities. They found the insula to be inexcitable even with strong currents and were unable to obtain vocalization. Conjugate movements of the eyes to the opposite side were obtained by stimulation in the frontal lobe and the occipital pole in regions (fig. 1) which must have corresponded roughly to Area 8 and Area 17 of Brodmann. Grünbaum and Sherrington found that postcentral removal produced no paresis and precentral extirpation caused a severe, but rapidly diminishing paralysis of the movements which electrical stimulation of that area had previously produced. They observed that the response from a cortical point might be "influenced by the particular forms of movement excited from neighbouring points just antecedently." They pointed out that a cortical point was, therefore, to some extent unstable and that by preliminary precentral stimulation a response from the post-central gyrus could be elicited. This process they called "facilitation." Graham Brown alone and with Sherrington followed up this problem at a later date (Brown, 1915, 1916), and showed that a spot stimulated might be sensitized by facilitation and that an echo response of secondary facilitation might be produced in a neighbouring point in the postcentral gyrus (activation). Furthermore, Graham Brown and Sherrington showed that a response might

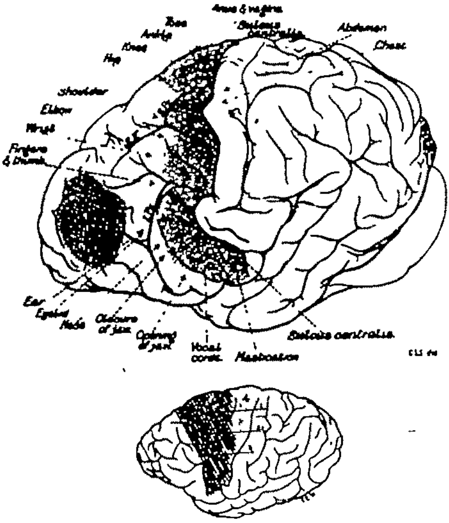

FIG. 1.—Results of cortical stimulation in the chimpanzee above (from Grunbaum and Sherrington, 1901). Cytoarchitectural localization of Areas 4 and 6 in the chimpanzee below (from Bucy, 1934). Comparison of the figures indicates that the isolated movements found by Grünbaum and Sherrington were not confined to Area 4 in the arm and face areas. Eye movements only were found from the detached frontal lobe centre. The same was true of the occipital centre for eye movement. Movement points end abruptly at the central fissure.

be qualitatively changed, i.e. from flexion to extension. This they called "reversal."

O. and C. Vogt combined careful cytoarchitectural studies with animal stimulation and produced for the monkey a map which resembles those of Grünbaum and Sherrington. By means of their cytoarchitectural studies of the human cortex they prepared a map of the human cortex and transferred functional localization points to it (1926). This map (fig. 2) corresponded to an extraordinary extent with that which Foerster prepared for man as the result of stimulation of patients, as indicated in the Vogts' publication just cited.

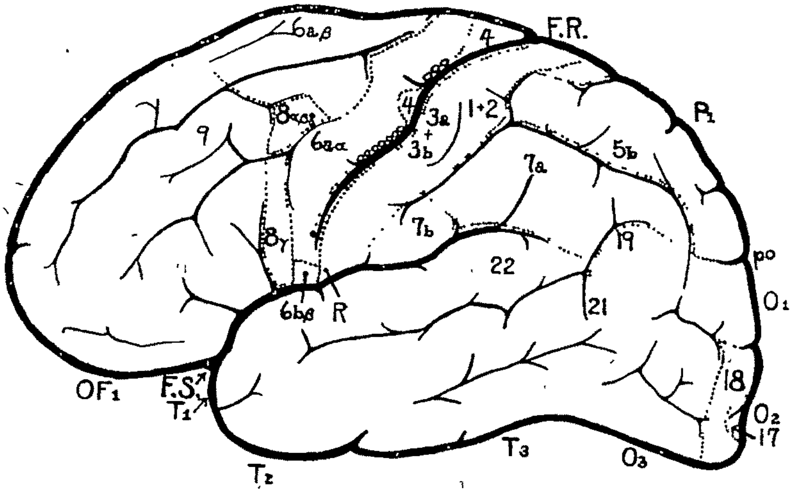

FIG. 2.—Cytoarchitectural fields of human cortex after Vogt and Vogt (1926). The functional interpretation is deduced by them from the homologous fields in monkey. F.R. = fissure of Rolando. F.S. = fissure of Sylvius. p.o. = parieto-occipital fissure. R. = respiration. 4 = true pyramidal cortex or "primary field for tonic specialized movement" 6*a alpha* = "secondary field for tonic specialized movements" which acts upon the primary field by conduction along the outermost layers of the cortex; 6*a beta* = tertiary field where stimulation most easily causes turning of eyes, head, ears and body to opposite side (adversive movements); stronger stimulation gives movements of both upper and lower extremities; 8 *alpha, beta, delta* = field from which adversive eye movements were most easily produced; field 3*a*, 3*b*, 1 and 2 = postcentral convolution producing movement by action upon field 4. 5*b*, 7*a* and 7*b*, all produce adversive movements with strong stimulation; 19 (also 17 and 18) = adversive eye movements. 22 = ear and eye adversive movements; 6*b* = mastication.

Recently Fulton (1936) and his associates, working upon monkeys and anthropoids, and using the fields of Brodmann and Vogt (fig. 2), have urged that the motor representation in the cerebral cortex is made up of: (*a*) motor area or Area 4 of Brodmann which gives origin to the pyramidal tract; and (*b*) a "premotor" area made up of (i) Brodmann's Area 6*a alpha*, which together with Area 4, composes the precentral gyrus in man; and (ii) Brodmann's Area 6*a beta* which in man lies anterior to the upper end of the precentral gyrus. Fulton used the term "extrapyramidal" motor cortex to indicate all of the cortex which might be motor in addition to Area 4.

The evidence from the study of human cases may be summarized as follows:—

Roberts Bartholow, an American surgeon of Cincinnati, is credited by Beevor and Horsley (1890B) with being the first to stimulate the human brain directly. It is true that Hitzig (1870A) had preceded his animal experimentation by indirect galvanic stimulation of the occipital region of a man, thus producing eye movements. The account of Bartholow (1874) is interesting to say the least and may be cited.

His patient was a 30-year old-domestic. As an infant this unfortunate had chanced to fall into the fire, burning her scalp so badly that "hair was never reproduced." A piece of whale bone in the wig she was forced to wear irritated the scarred scalp and, by her statement, three months before she was admitted, an ulcer appeared. When she presented herself for relief, this had eroded the skull over a space 2 in. in diameter "where the pulsations of the brain are plainly seen."

Although "rather feeble-minded" Bartholow observed that Mary returned replies to all questions and no sensory or motor loss could be made out in spite of the fact that brain substance apparently had been injured in the process of evacuation of pus from the infected area. The doctor believed, therefore, that fine insulated needles could be introduced without further damage.

First he observed that no pain was experienced from the brain substance proper and that mechanical irritation yielded nothing. Faradization of the dura "with the least possible current" produced muscular contractions of the opposite arm and leg, and head turning to the opposite side.

One of the needles was then passed into "the left posterior lobe so that the non-insulated portion rested entirely in the substance of the brain," the other needle resting on the dura. There was produced a muscular contraction of the right upper and lower extremities with "faint contraction of the orbicularis palpebrarum and dilatation of the pupils." She also complained of a "strong and unpleasant tingling in both opposite extremities, especially the arm, which she seized with the opposite (left) hand and rubbed vigorously." A similar manœuvre on the right side produced similar results.

While the electrodes were in the right side Bartholow decided to try the effect of more current. "Her countenance exhibited great distress and she began to cry. Very soon the left hand was extended as if in the act of taking hold of some object in front of her; the arm presently was agitated with clonic spasms; her eyes became fixed with pupils widely dilated; the lips were blue and she frothed at the mouth; her breathing became stertorous, she lost consciousness and was violently convulsed on the left side. This convulsion lasted for five minutes and was succeeded by coma. She returned to consciousness in twenty minutes from the beginning of the attack and complained of some weakness and vertigo." Three days after this stimulation, following a series of right-sided seizures, the patient died.

Sciamanna's results in 1882 were similar (see Beevor and Horsley, 1890B). Horsley (1887), Keen (1888), Nancrede (1888), Lloyd and Deaver (1888), Parker and Gotch (1893) and Bidwell and Sherrington (1893) corroborated in the human the motor responses previously obtained from the motor cortex of animals. In 1892 Ransom stimulated the cortex of a conscious patient and produced both sensation and movement.

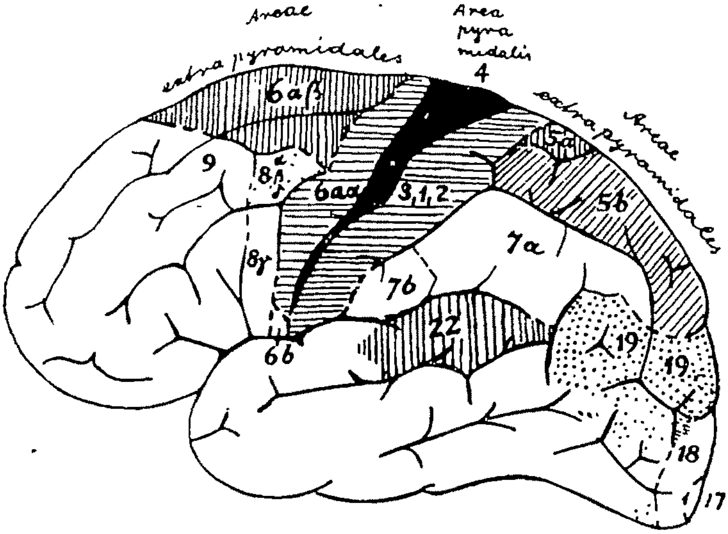

FIG. 3.—Extent of motor cortex in the human brain, after Foerster (1936). The cortical areas for motor response to electrical stimulation are outlined. The numbers refer to the cytoarchitectural fields of the Vogts described in fig 2. Mass movements and adversive movements are reported from the extrapyramidal areas including 6a *beta*, 5 and 22. Movements from the pyramidal area are distinctly isolated in character. The extrapyramidal system produces mass movements of the opposite side, according to this author.

Cushing (1909) was the first to produce sensation without movement in man. He stimulated the postcentral gyrus of two conscious patients each of whom reported sensations in parts corresponding with areas where movement could be produced from analogous precentral regions. Van Valkenburg (1914) corroborated these findings.

Foerster (1936A and B), as the result of stimulating the human cerebral cortex, chiefly under local anæsthesia in cases of focal epilepsy, widely extended the motor cortex (fig. 3). He pointed out that the "precentral areas are chiefly motor and the postcentral convolution is chiefly sensory," but he included the postcentral convolution as motor in a sort of secondary category.

In general agreement with Fulton, Foerster added a frontal extra-pyramidal motor area ("6*a beta*"), a parietal extra-pyramidal area ("5") and a temporal extrapyramidal area ("22"). He stated that even in the absence of the pyramidal zone 4 these areas (as well as Area 6) were capable of producing a mass movement of the opposite side of the body when stimulated strongly by a faradic current. In the intact brain the post-central gyrus was able to produce isolated movements with a higher threshold than the precentral, but when Area 4 was absent this response ceased and only the mass movement described above was produced.

(3) Clinical Material.

The observations reported here were made during operations carried out since 1928 by one of us (W.P.).[1] Of the 163 operations in which cortical stimulation was carried out, 126 proved to have records suitable for the present analysis.

In general, stimulation was only carried out in any operation when there was therapeutic justification for it. In some instances it was used to define the motor area of the hemisphere so that an infiltrating tumour could be removed as widely as possible without producing paralysis. More frequently stimulation was made use of as a preliminary to radical extirpation of an epileptogenic focus and as an aid in searching for that focus. The actual therapeutic results of such operations are completely summarized elsewhere (Penfield, 1936).

However, in the therapeutic approach, it should be pointed out that only very rarely has the Rolandic area been included in any excision and never has this region of the brain been touched unless a lesion was present that could be demonstrated grossly by operative inspection. This digression is made in the hope of discouraging surgical removal of normal brain from the Rolandic area, or elsewhere, whatever may have been the pattern of epileptic seizure.

The operations have been carried out as follows :—

Sterilization of scalp: local injection of nupercaine in solutions of 1 : 1,500 and 1 : 4,000 to which adrenalin is added. The sterile towels are then arranged perpendicularly so that the patient is cool, can see and move freely, and can be observed constantly. The rôle of anæsthetist is most important even though a general anæsthetic is rarely given, and in all of the records found in this communication we are indebted to our anæsthetist, Miss Mary Roach, who constantly followed the behaviour and movements of the patients as well as their blood-pressure, pulse and general condition through the long and sometimes trying ordeal of electrical exploration of the cerebral cortex.

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[1] Thirteen of the reported operations were carried out by our associate Dr. William Cone and are included here by his kind permission.

Osteoplastic craniotomy is used to expose large areas of the hemisphere, and the bone is replaced at the close of operation. The exposed brain is kept warm by the heat of lights focussed upon it, and moistened with Ringer's solution applied with an atomizer.

Stimulation is carried out by either unipolar or bipolar platinum electrodes which emerge from a glass handle and are attached to insulated wires, all of which may be autoclaved. Formerly we used a galvanic current for localizing purposes and a faradic coil to induce seizures. In recent years we have found a thyratron stimulator, similar to that described by Schmitt and Schmitt (1932), much more satisfactory and have usually employed a wave frequency of from 55 to 65 per second. This instrument is to be found now in use in physiological laboratories. It produces a current which resembles the faradic current of an induction coil, but here the thyratron tube filled with mercury vapour acts as the interrupter. The current is thus constant and may be altered accurately in rate and intensity.

It is essential that the patient should be in sympathy with operator and anæsthetist, and it is an interesting comment on the bravery and fortitude of mankind that almost without exception these subjects have gone through the ordeal of operation patiently and intelligently, even when young children. But however great may be their power of introspection, we make it a rule to restimulate all doubtful points without warning. Responses which cannot be reproduced, especially unusual ones, are eliminated.

Beginning with a subliminal stimulus, the strength is increased until a positive response is obtained. The threshold of the postcentral convolution is usually below[1] that of the precentral, although they are often the same. It is usually best to outline the Rolandic fissure thus before exploring further. Each time a positive response is obtained a small square of paper bearing a number is placed upon the brain at that point. These numbers or letters, beginning at 1 or A, indicate the order in which positive responses were obtained.

After outlining the fissure of Rolando the intensity of current is then increased and exploration carried further afield over the cortex. No record of the position of negative stimulations is made.

Details of the electrical exploration are recorded by a running dictated description from the surgeon to a stenographer who is present at this stage of the operation. She records the number of the stimulation, description of the response and the time of each. Photographs are taken in a camera outside the operating theatre through a mirror placed above the operating table (described by Hayden, 1936). The surgeon, with sterile paper and pencil, also makes a sketch at the close of stimulation, placing the numbers where he thinks they should fall upon a uniform life-size brain diagram like that employed for the charts in this communication. On this sketch he measures the distance from central fissure and from the fissure of Sylvius for each number.

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[1] Foerster has found the reverse to be the case.

(4) METHOD OF ANALYSIS.

Auditory, visual and olfactory responses have been eliminated from this report. Analysis of the drawings, photographs and operative notes has been made by one of us (E.B.) as follows:—

A separate summarizing chart was made for each individual movement or sensation produced by stimulation. For example, all movements of the thumb obtained by stimulation in the right hemisphere were placed on one chart with the reference number of each case. Movements of the thumb from the other hemisphere were first charted separately in like manner, and the index finger and other members similarly. When found to be alike the results from the two hemispheres were then combined for each member. Unilateral and bilateral responses were separately recorded.

Each operation in the series was given a number, and as the results were transferred from the operation records to the summarizing charts the operation number was placed beside each of its points, thus making it possible to refer back from the common movement or sensation chart to the operation report if desired. No movement or sensation which was part of a definite epileptiform seizure has been included here as a sensory or motor phenomenon.

In transferring the stimulation points they have been placed on the common chart by reference to photograph and sketch according to their distance from the Rolandic fissure. From above down the points were placed in proper orientation according to the distance from the Sylvian and the median longitudinal fissures. These are the only landmarks on the brain surface which can be recognized with any degree of accuracy. Indeed, the Rolandic fissure can hardly be recognized until after stimulation has identified it. Estimation of position was necessary in a few of the earlier drawings. In the large majority of instances, however, direct measurements and photographs have made the exact topographical localization of the points as accurate as is possible.

In this way 170 summarizing charts were made which have been condensed into the sixteen illustrative charts reproduced here. All results have been transferred to the right hemisphere for the sake of uniformity and brevity.

(5) ILLUSTRATIVE CASE.

One operation record may be described here in detail as an example:—

Case 110.—M. G., a girl aged 21, suffering from Jacksonian seizures beginning with a sensation in the left hand. Right osteoplastic craniotomy; nupercaine analgesia, June 9, 1936. An area of abnormal brain was excised, the area being quite small and limited almost altogether to the postcentral gyrus. The procedure has not, alas, resulted in cessation of attacks. The report follows.

"*Objective Findings.*—The dura was under slightly increased pressure and the bone was unusually indurated. There was a scalp scar in the posterior parietal region and a great deal of thickened tissue underneath the scalp, showing that there had been a considerable subaponeurotic hæmorrhage at some time or other. The brain seemed to be normal excepting that the gyri in general were a little small. It was noted that one gyrus was slightly yellow and somewhat flattened and that just below this yellow area the gyrus was extremely narrow; this proved, on stimulation, to be the postcentral gyrus and the actual focus from which the attacks were coming. The extreme narrowing seemed to be slightly below the focus from which the attack could be produced and the narrow area corresponded with the letter "K" which produced sensation in the thumb and running over toward the index finger. This was the most satisfactory response as far as postcentral gyrus was concerned."

"I think that even a greater subdivision of responses could have been obtained if time had been available. The same weak strength of stimulation, namely 24, was used all along the motor gyrus without producing any tendency toward an attack. The three attacks were all produced within a short radius in the abnormal convolution."

"*Procedure.*— A moderate sized osteoplastic flap was turned down posteriorly, the dura was opened and after the electrical exploration an oval incision was made in the brain about the epileptogenic focus. Cutting with thread, the incision was carried down to a depth of about 1½ cm. It was noted that after the threads were tied, outlining the block to be excised everywhere except at the bottom, there was no reduction in the strength of her grip; this in spite of the fact that the area must have been cut round quite well. After removal of the block of tissue, however, she lost almost complete use of her hand." (See dictated note below.)

"The removal was practically all postcentral but it must be noted that there was some injury to the precentral gyrus but not to a depth of greater than 2 to 3 mm. and over an area not greater than 1 cm. in length. All devitalized tissue was removed. The dura was closed excepting under the temporal muscle where a small decompression was left. The bone flap was fastened with steel wire at two points mesially and left free below. The aponeurosis and skin were sutured by Dr. Walker."

Dictated Record of Stimulation.

(Stimulating thyratron intensity 30, raised to 24 from B on; frequency about 65, bipolar electrode; letters and numbers laid on brain as shown in fig. 4. The following record is given as dictated but quotation marks are used only to signify the patient's own words.)

Four negative stimulations.

A. Pain in right side of face; unable to secure this from dura adjacent.

Repeated twice—failed twice, should be ignored.
Two negative stimulations.

B. Arm and hand "feels as though it was going to sleep."
Repeated once without warning.

C. Numbness left side above umbilicus. This location seems to be epigastric.

D. Sensation in right arm and hand; when repeated, said to be more in arm.

E. Sensation in hand and fingers; when asked what the sensation was like she replied: "like going to sleep." When asked if it was numbness or tingling, she replied "Both."

F. Sensation in ring and little finger.

G. Sensation in same fingers.

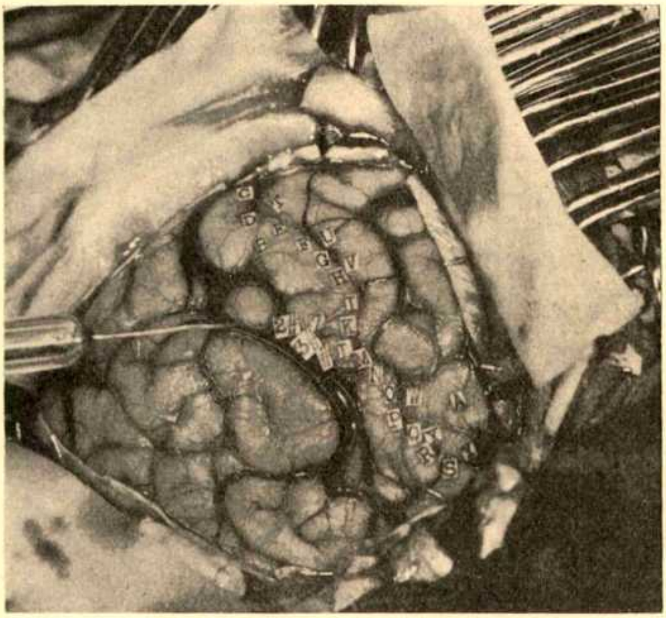


FIG. 4.—Cerebral cortex in Case 110 photographed during operation. The tickets of reference indicate responses which are described in text. *See* fig. 24 for diagram of same case.

Changed from Bipolar to Unipolar Electrode.

11 a.m. Left leg "going to sleep"—no stimulation.

H. Same feeling in index and large fingers.

I. Sensation in index finger—same feeling.

K. Sensation in thumb.

L. Sensation in thumb and toward index finger, but not in that finger.

M. Sensation left side of face—numbness.

N. Patient laughed a little; sensation in lower left lip.

O. Lower lip, left side.

P. Upper and lower teeth and gums.

Q. Left side of tongue and tip.
R. Tip of tongue, left side.
S. Back of left side of tongue.

Three negative stimulations.

T. Marked flexion of forearm on arm.
Repeated—no sensation. Same just above "T."
U. Inward rotation of hand and arm and slight flexion of fingers.
Indefinite sensation of numbness in hand and fingers.

One negative stimulation.

V. Slight flexion of hand and fingers; no sensation.

Two negative stimulations.

W. Mouth drawn to left and downward; no sensation.
X. Tongue drawn downward and to left; no sensation.
Y. Tongue drawn to left; movement of neck to left.
No response between "V" and "W."

Two negative stimulations.

11.10 *a.m.* *Attack following stimulation at* ♯.—Patient said she had sensation in the left thumb; next that it was going to the hand: next up the arm. Then convulsion characterized by slight convulsive movement of left hand and arm. Her first observation at the end was "Did he see it? I have had an attack." Pulse at wrist present throughout attack. Slight confusion at close and restlessness. No clonic movements elsewhere. Duration from sensation in fingers to her question after the attack was 1 min. 54 secs. In the brain it was observed that the hemisphere as a whole was pulsating during the attack. At least one artery was observed not to be pulsating during the attack. This artery showed visible pulsation at the close. An artery further posterior was also seen to begin to pulsate at the close of the attack.

11.17 *a.m.* *Attack* 2.—Patient was silent. Change in circulation of brain was noticed and spoken of before we realized an attack was starting. I do not know how to describe the alteration. A few seconds later Miss Roach stated that an attack was beginning. Brain then bulged and for a few seconds there was no pulsation in the cerebral arteries. Pulsation in the arteries began before the end of the attack and the brain began to recede. Pulse was present in wrist all the time.

Patient was not conscious that she had had an attack but she remembered that she had had sensation in thumb and then that it was going to her fingers. Stimulation producing each of the attacks was no longer than one second. Three negative stimulations.

Z. Sensation in thumb.

Experimental activation (*or secondary facilitation*).—Stimulation on the anterior margin of the precentral gyrus at level of T in figure 4 gave no response. Stimulation at T gave marked flexion of elbow as previously. This stimulation was then followed at one second intervals by a succession of stimuli which advanced anteriorly across the convolution to the anterior margin of the gyrus. Each stimulation was followed by elbow flexion of about the same intensity. This movement was thus produced from an area which had previously refused to give movement. The same thing was repeated in the postcentral gyrus. Thus a sensation in the arm was produced at D and reproduced by each successive stimulus back to the posterior margin of the gyrus, although there had been no sensation when the posterior margin had been previously stimulated.

Attack 3 —Same as time before. Did not know she had one. Followed by slight emotional change and flushing of face. There seemed to be a variation in pulsation of the arteries. Pulse felt in wrist continuously. Duration of third attack thirty seconds.

Examination following excision.—Immediately after all the cutting sutures were tied the patient was able to squeeze the dynamometer up to 13 with her left hand, while she could do it up to 15 with her right hand. After the extirpation, however, she could not squeeze the dynamometer at all although she was able to extend her wrist, just causing the hand to close a little. On leaving the operating room I found that pricking with a needle of any one of her fingers or thumb gave her pain and she was able to localize it to the proper digit. However, if any of the digits were pinched, moved or touched she had no intimation of it. She did not seem to know where her hand or arm was. On showing her teeth there was possibly a very slight weakness of the left side but nothing more than that.

(6) TOPOGRAPHICAL ANALYSIS.

The responses for each subdivision of the body are analysed separately below and summarized in accompanying charts. Points which are widely displaced from their natural groupings can usually be explained by "epileptic spread" which will be discussed under a subsequent heading, or by the gross cerebral deformation due to a pre-existing lesion.

(7) MOVEMENTS OF THE TONGUE (fig. 5).

There are sixteen accepted points producing tongue movement in this series. Thirteen of these are precentral and three are postcentral. Ten points, including all of the postcentral ones, are from the left hemisphere. Because of the tongue's objective inaccessibility its movements can be discovered only through voluntary information from the patient, so that some movements may have been missed. For the same reason it was impossible in most instances to record the exact type of movement whether contralateral, ipsilateral, or bilateral.

Only point 44 is very far removed from the fissure of Rolando. This was the case of an epileptic who had a bilateral cerebral lesion. Point 18 from the same patient was found on the opposite hemisphere. On neither side did the point seem to be displaced by an "epileptic habit." Point 40 may perhaps have been displaced by the patient's lesion, an infiltrating glioma.

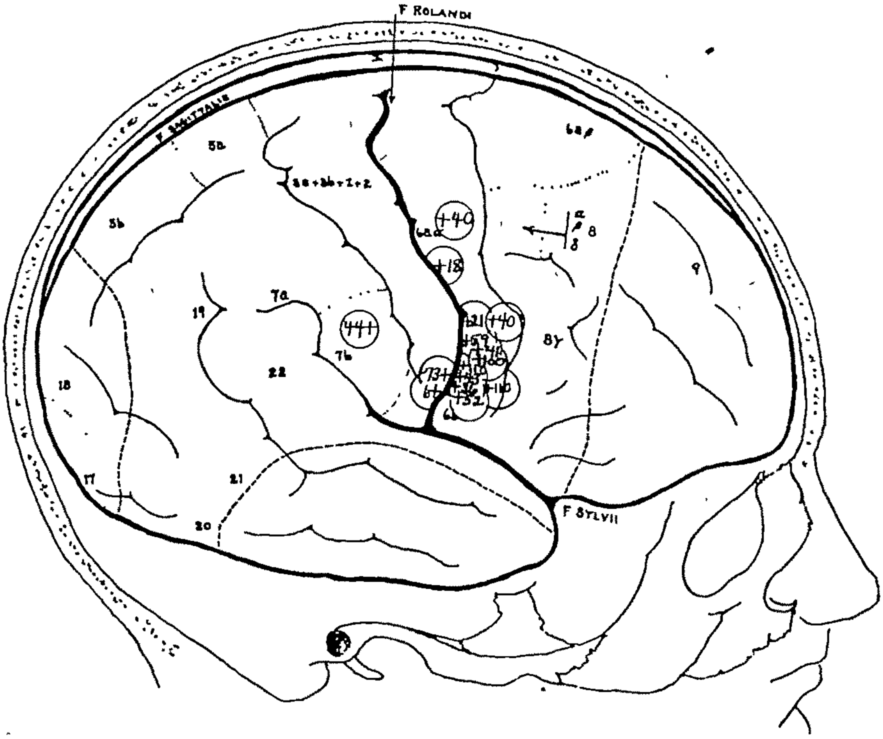


Fig. 5.—Movements of the tongue.

(8) Sensation in the Tongue (fig. 6).

Patients show great capacity for exact localization on the tongue. The information received has resolved itself into six groups listed as contralateral side, tip, middle, base, place not stated and taste. There is a total of 99 postcentral, 24 precentral, and 2 superior temporal points.

The sensation was recorded as contralateral side 48 times, of which 39 are postcentral, 8 are precentral and 1 is temporal. Twenty-three postcentral, 3 precentral and 1 temporal point gave sensation at the tip. There was feeling in the middle of the tongue during 8 postcentral and

4 precentral stimulations. Two postcentral and 2 precentral points gave a sensation at the base.

The exact point on the tongue was not stated in 33 instances, 26 postcentral and 7 precentral. In one instance only (postcentral) the sensation was on the ipsilateral side. Twice the sensation was that of movement. One precentral point gave a feeling of "inability to control my tongue."

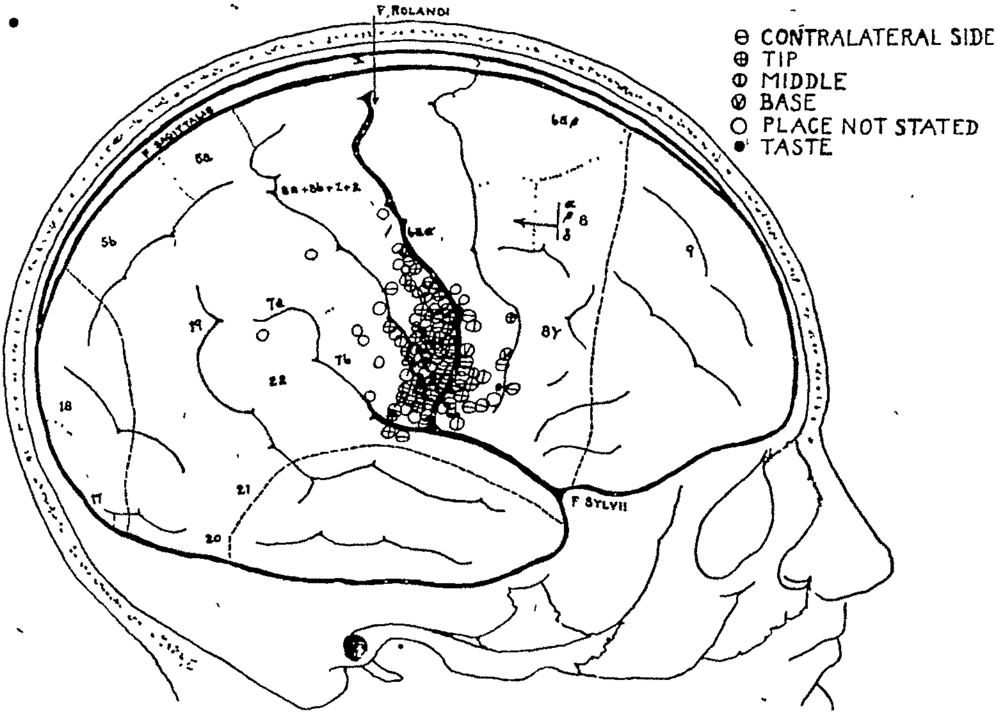


FIG. 6.—Sensation in the tongue.

In five cases the patient described the sensation as being one of taste. Four of these points were postcentral and one precentral. The particular kind of taste was not described. The two points beneath the Sylvian fissure were checked without warning with the same result.

The fact that points on the chart take up space gives the impression that the cortical points extend farther from the Rolandic fissure than is often the case. Usually the responsive areas were very near the anterior lip of the postcentral gyrus. It is obvious, however, that the region may extend one and one half centimetres behind the central sulcus and the same distance in front of it.

Bilateral and ipsilateral sensations are more frequently encountered in the tongue than in any other part of the body. In those cases, seven in all, where sufficient detail was available, it was found that the tip of the tongue had a position on the cortex above the side and base in five instances, and below the side and base in two instances.

(9) MOVEMENT AND SENSATION IN THE MOUTH (fig. 7).

For the mouth and lips there are 3 postcentral and 18 precentral motor points to be compared with 21 precentral and 53 postcentral points for sensation. The sensations reported were described much as

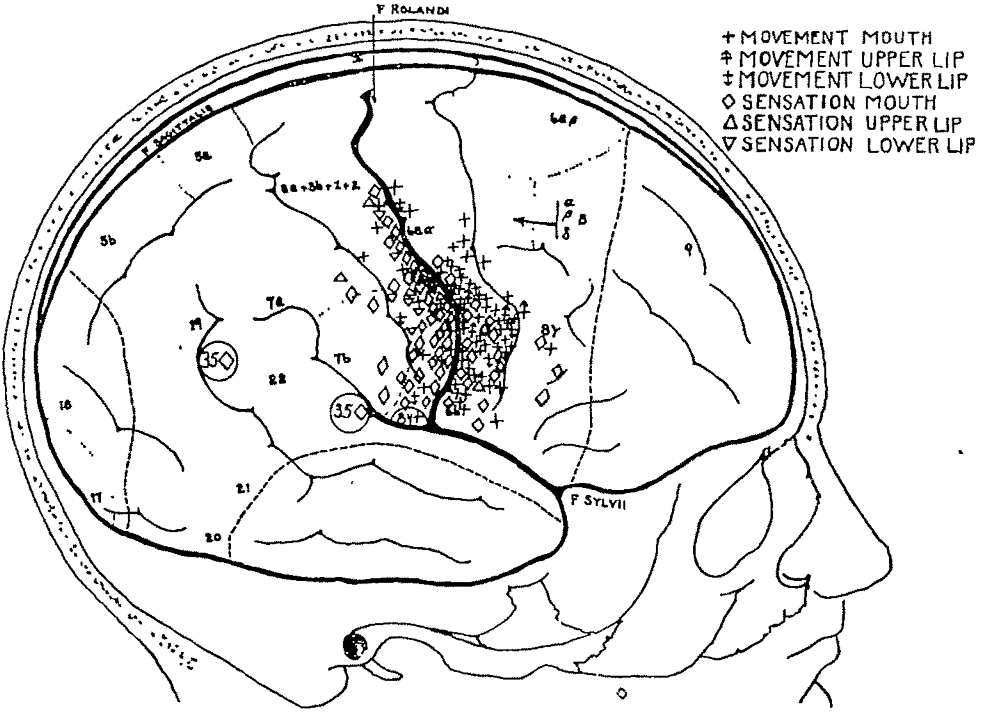


FIG. 7.—Movement and sensation of the mouth.

elsewhere, usually as tingling or numbness. Movements have been most often twitching in character, but also opening and closing, smacking, sucking and trembling of the mouth. Ipsilateral lip movement occurred eight times.

Special attention should be called to the comparatively large number of precentral sensory and postcentral motor points in this group. It is also of interest that the sensory localization extends farther, both anterior and posterior to the fissure of Rolando. Motor point 84 (near the inferior end of the postcentral gyrus) was the sole motor response from this patient. Shortly before operation she had developed a hemiplegia following status epilepticus.

(10) Jaw Movement and Sensation within the Mouth (fig. 8).

For the purposes of this chart "in the mouth" means in the teeth, palate and jaws. There are 40 postcentral points and 16 precentral points which have produced such sensation. Ipsilateral feeling has been moderately frequent. One point gave a sensation of cold. None of these patients experienced pain in jaws or teeth, but usually numbness.

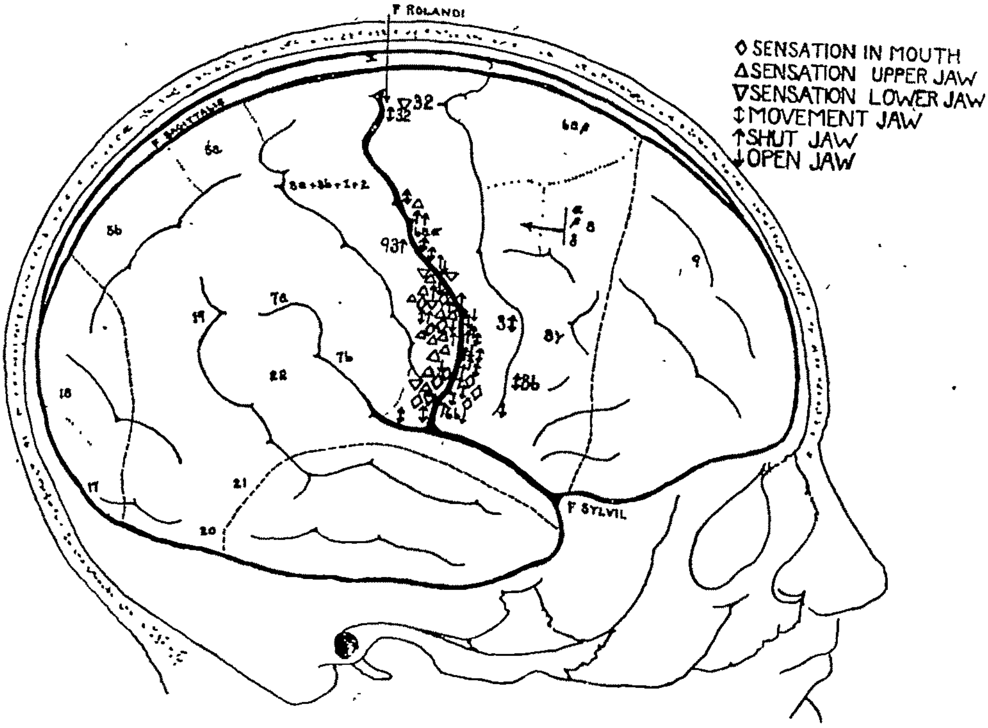


Fig. 8.—Jaw movement and sensation within the mouth.

Forty-one points produced jaw movement. Twenty-nine of these were precentral and the remainder were postcentral. Simple "jaw movement," which usually means opening and closing, occurred 25 times, 19 of which followed precentral stimulation. Six precentral and 4 postcentral points produced jaw closing; 4 precentral and 2 postcentral points produced opening of the jaws. With two exceptions all of these points are within a centimetre of the Rolandic sulcus.

The points 32 are obviously well away from the general centre.

The scar in this epileptic subject was over 4 cm. below and in front of these points. It is doubtless an example of displacement of response due to habitual epileptic discharge, a subject to be discussed presently.

(11) Movement and Sensation of Face (fig. 9).

The striking thing about this chart is the relative rarity of motor response from the postcentral gyrus as compared with other areas of the body. Thirty precentral and one postcentral points produced eyelid movement; of these, eyelid closing was the most frequent response. Other common movements were twitching and opening of the lids. Twelve other motor responses were simple "face" movements, usually twitches and including nose and brow. The four atypical points of case 78 were thoroughly re-checked. There were no other points in the vicinity which could give this response.

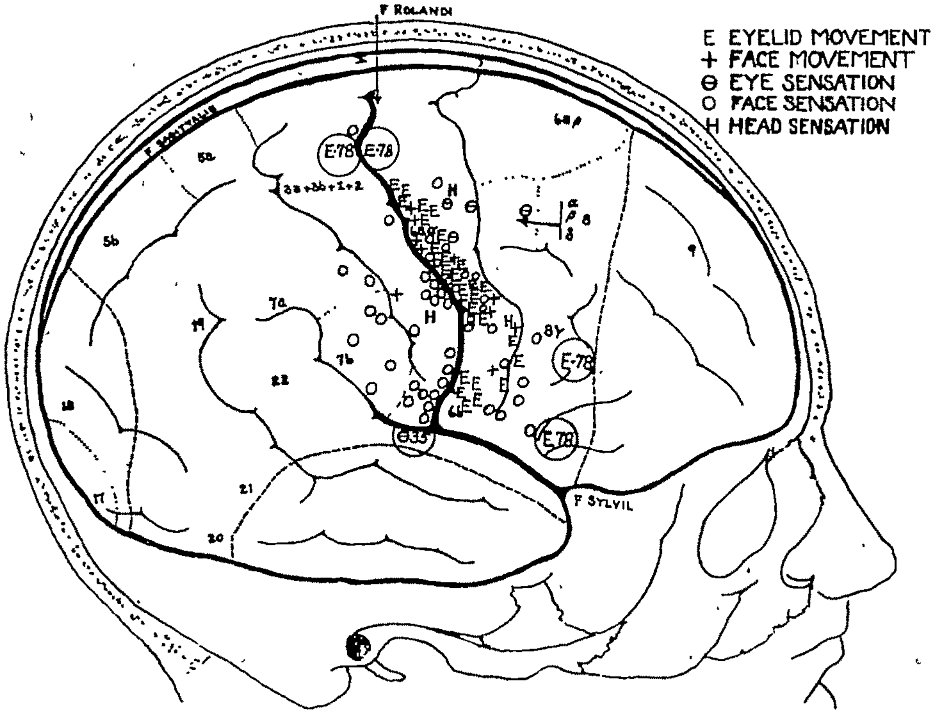


FIG. 9.—Movement and sensation of the face.

Somatic sensation in the eye occurred after four precentral and one temporal stimulation. Sensation in the remainder of the face was quite common. There are 20 precentral and 24 postcentral points on the chart. There is a suggestion of a grouping of these face sensations at the inferior end of the postcentral gyrus.

One motor point in Case 118 produced elevation of the opposite brow, opening of the opposite eyelid and turning down of the corners of the mouth. This was not part of an habitual epileptic pattern. It seems to have been a grimace activated from a single motor point.

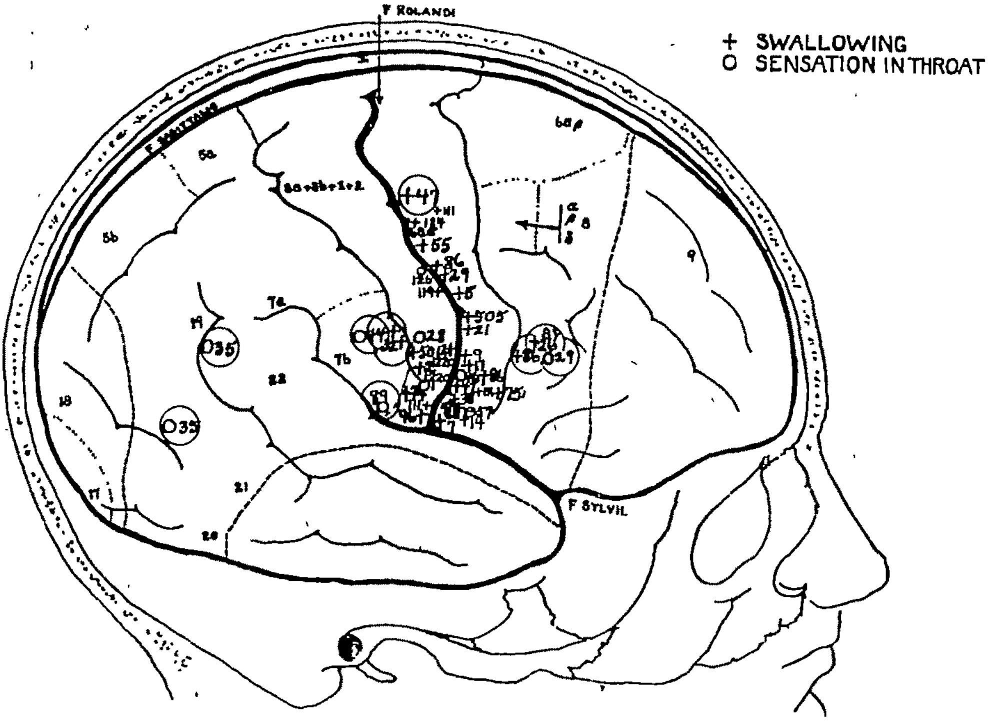


FIG. 10.—Swallowing and throat sensation.

(12) SWALLOWING AND THROAT SENSATION (fig. 10).

It has been necessary to exercise great care in the distinction of spontaneous swallowing from swallowing as a response to cortical stimulation. There were 32 examples of definite swallowing secondary to stimulation. Of these 23 were from precentral points. This means proportionally a much greater number of postcentral motor points than for face.

Throat sensation resulted from nine postcentral and four precentral points. Even when the grossly atypical location of the stimulation point of Case 35 is ruled out, these sensory points are spread over a much wider territory than are motor.

In Case 35 the response is doubtless displaced by a very large cyst posterior to these points from the margin of which epileptogenic discharge, evidently took place. The patient described the sensation produced as " a feeling of filling up in the throat."

(13) Vocalization (fig. 11).

Six examples of vocalization included in this series were published by Penfield (1937) as the first example of such a response to stimulation of the cerebral cortex. We have been most interested in the rather sharply localized area for vocalization which is shown in this chart. In most cases, the response is obtained from a small area of a few millimetres in diameter. Once the area extended in a narrow band across the precentral convolution.

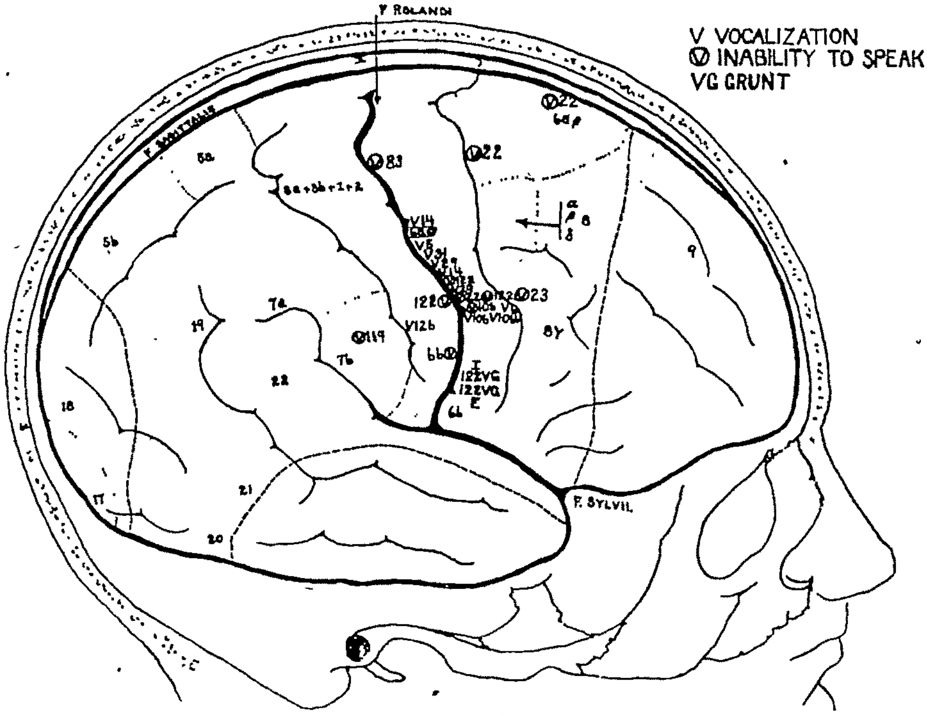


FIG. 11.—Vocalization.

Vocalization may be produced by cortical stimulation in the precentral gyrus on either hemisphere. It was produced four times from the dominant and four times from the non-dominant hemisphere. It occurs without any associated motor phenomena. Its localization is between the area for eyelid movements above and mouth below.

The response may be illustrated by some of the findings in Case 14. This was the first example of vocalization encountered, and surprised the surgeon quite as much as the subject. Two discrete points were found near each other in this patient. The upper point in this patient was stimulated thirty-one times in succession and vocalization was the response each time. There was nothing to suggest the formation of words. The patient was unable to stop the cry or to influence it in any way, even when urged to do so. Stimulation at points a few millimetres distant gave no response. The second point lower down on the gyrus (V-14, fig. 11) gave vocalization, but at a definitely lower pitch. At the intensity used no movements could be elicited anywhere over the cortex. That is, the stimulation threshold was lower for vocalization than for anything else in this case.

In Case 122 it will be observed that inspiratory and expiratory sounds (122 VG, fig. 11) were produced from adjacent points. Both of these sounds, however, were grunts of short duration and were associated with sensation in the mouth. The expiratory grunt was repeated. These are not examples of true vocalization as found in the other cases. They resemble rather the grunt which has been reported by Foerster and others previously, but not the loud continuing cry of true vocalization.

In vocalization the sound continues if the stimulation continues until the patient's breath expires, when he may take a breath and cry again. Usually the vocalization is an expiratory vowel sound. The three points for 106 which are distributed across the precentral gyrus were adjacent to another point from which the sense of inability to speak was obtained. Only one vocalization point has been found on the postcentral gyrus.

The patient's subjective feeling of inability to speak, indicated by the letter " V " in a circle in fig. 11, has been elicited from a scattering of points which became more numerous near the vocalization region. These evidences of inhibition are not associated with convulsive discharge. Inability to speak was subjective as a rule. Patient 22, however, was told to count aloud and, while doing so, appropriate stimulation caused a definite hesitation, though it did not completely stop her. Afterwards she volunteered that it had been difficult to speak when she had been about half way through. Others have stopped counting, or have volunteered that they could not speak.

(14) HEAD SENSATION.

No chart is made for this group. Out of the 11 responses called head sensation 6 were characterized as painful. Of these 6 responses, 3 were ipsilateral, 2 frontal and 1 not stated. It seems apparent, therefore, that all of these painful sensations are to be looked upon as evidences of referred pain from stimulation of the brain as an organ. This would seem to be contradictory to the statement made elsewhere by one of us (Penfield, 1934), that the brain is insensitive and pain within the skull is produced only by stimulation of dural sinuses, large dural arteries and deep in the fissure of Sylvius where the middle cerebral artery enters it.

In a case where stimulation of the hemisphere does produce pain or headache, the pain or headache comes from numerous points, showing that it is not a matter of cortical activation. Such pain is very rare, but it does exist. There were two other ipsilateral sensations in the general group which may also be considered as referred sensation.

This leaves only three contralateral head sensations which seem to be evidences of sensory head representation. To these may be added two contralateral neck sensations. All five of these points fall roughly into the general vicinity of the face area and are recorded in fig. 9 as H.

Head aura occurred eleven times. That is to say a head sensation was produced which was characteristic of the patient's habitual epileptic aura. This aura seemed to have no localized representation, but occurred from points spread widely over the hemisphere.

(15) MOVEMENT OF FINGERS (fig. 12).

Finger movements are among the best localized of the responses found in this study. Although the responsive points extend 5½ cm. along the length of the fissure of Rolando, very few are found more than 1 cm. distant from it.

Of the 102 recorded points, 77 are precentral and 25 are postcentral. The most common response was movement of all the fingers together. It seems likely that this may be looked upon as an individual movement, not a combination of separate movements with individual representation. This occurred from 45 precentral and 12 postcentral points. Flexion of the individual fingers followed 23 precentral and 4 postcentral stimulations. Extension was the response from 16 precentral and 4 postcentral. The other movements were twitches or were not described in detail. The thumb was next in frequency of response with 15 precentral points and 6 postcentral. The order of frequency of individual fingers or combinations of fingers in this series is as follows. Index, 4 precentral and 1 postcentral; little, 4 precentral and 1 postcentral; ring and little, 2 precentral and 2 postcentral; index and middle, 2 precentral and 1 postcentral; middle, ring and little, 3 precentral; thumb and index finger and ring finger, 1 each precentral and postcentral.

It was interesting to note that the only grouped finger movements were of the thumb and index, the index and middle fingers, the ring and little fingers, and the middle, ring and little fingers. We were surprised that the point for so useful and used a digit as the index finger was not encountered more frequently. It responded no more frequently than the little finger.

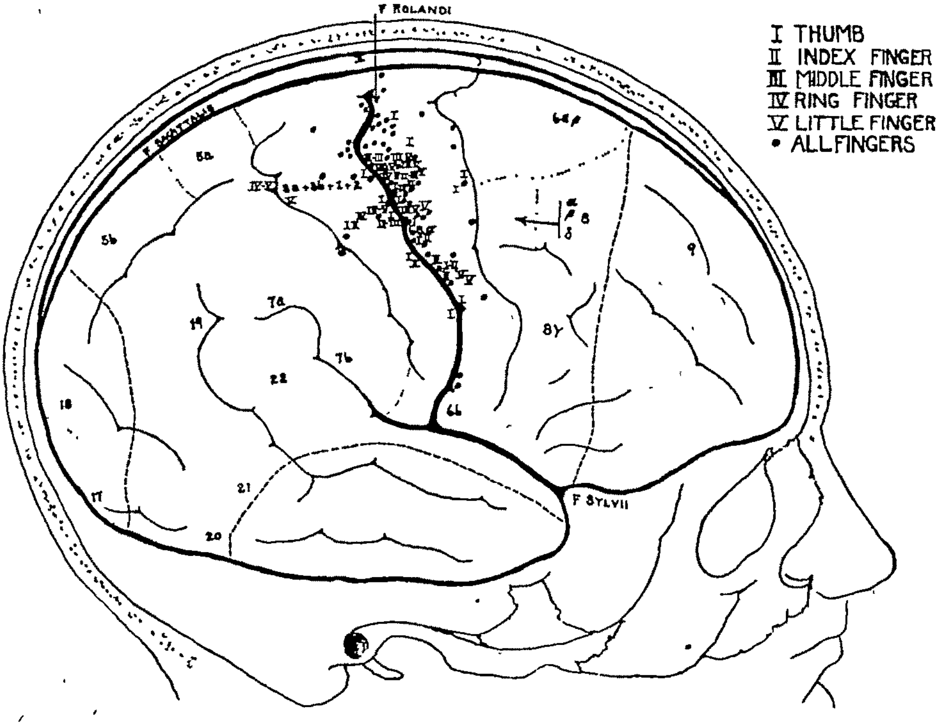


FIG. 12.—Movement of digits.

Flexion and extension responses were often separable in an individual case, and points for one digit were sometimes found separated rather widely as though these members had a comparatively large amount of cortex devoted to them. Patient 118 had some interesting finger responses. One point produced extension of the index finger together with flexion of the thumb on the palm. Three other points responded with extension of all of the fingers and flexion of the thumb on the palm. But in this case an epileptogenic focal lesion lay near the finger area sensitizing it.

(16) SENSATION IN FINGERS (fig. 13).

At first glance the striking feature on this chart is the comparatively small number of precentral points. Even so, they constitute over one-sixth of the total, for of the 158 points 130 lie behind the Rolandic fissure and 28 in front of it. They extend along the edge of that sulcus for about the same distance as the motor points, and are limited to a strip of surface cortex unusually narrow for sensory points when compared with the extensive spread already seen in previous sensory charts.

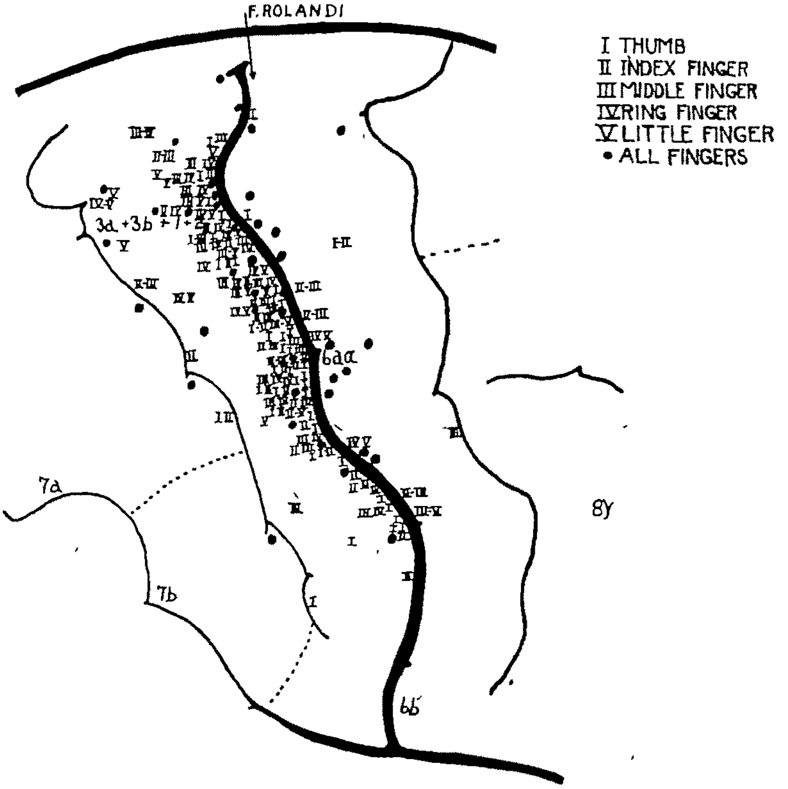


FIG. 13 —Sensation in digits.

On forty occasions the patient felt sensation in all of the fingers. Twenty-seven of these points are postcentral and 13 precentral. In forty instances there was thumb sensation, 34 from postcentral and 6 from precentral points. The remaining points are distributed as follows: index finger 13, index and thumb 10, index and middle 9, ring and little 9, middle and ring 12, little finger 7 and middle finger 5, ring finger 3, middle, ring and little finger 5, index, middle and ring finger 3, and thumb, index and middle finger 2.

We also have remarked that here, as well as in finger movement, multiple finger response has been seen only in consecutive digits. Painful sensation accompanied two of these stimulations, both points being postcentral. Sense of movement was present with 4 postcentral and 1 precentral stimulations.

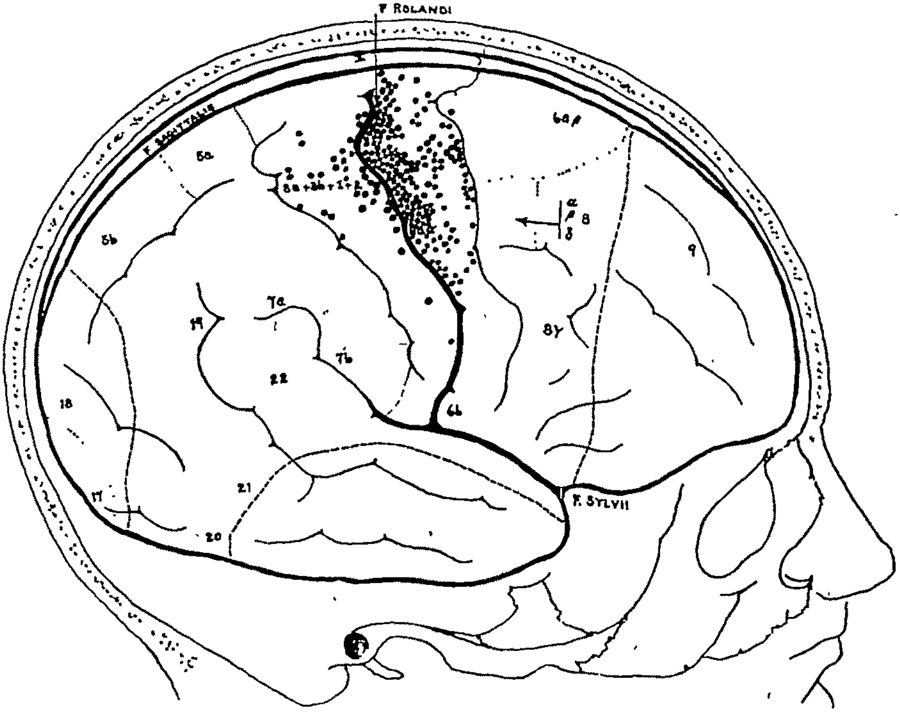


Fig. 14.—Movement of hand, arm and shoulder.

(17) Movement of Hand, Arm and Shoulder (fig. 14).

From practically the same general cortical area as that from which we have already reported finger movements there appear those of hand, arm and shoulder. Two hundred and twenty-two of these responses appear and but thirty-six of them are postcentral. There is a curious subgrouping of responses between 1 and 2 cm. in front of the central fissure.

The joints represented in this chart are metacarpophalangeal, wrist, elbow and shoulder. Metacarpophalangeal joint movement has been described regularly as "movement of the hand" by persons reporting the objective responses at operation, and has been transferred to the charts as such. There are 71 precentral and 22 postcentral cortical motor points for hand movement. Forty stimulations produced flexion and 11 extension. The remaining movements were not further described.

In the arm proper 39 stimulations produced wrist movement, 67 gave movement of the elbow and 23 resulted in shoulder movement. Ulnar deviation of the wrist occurred once. Flexion was four times as frequent as was extension.

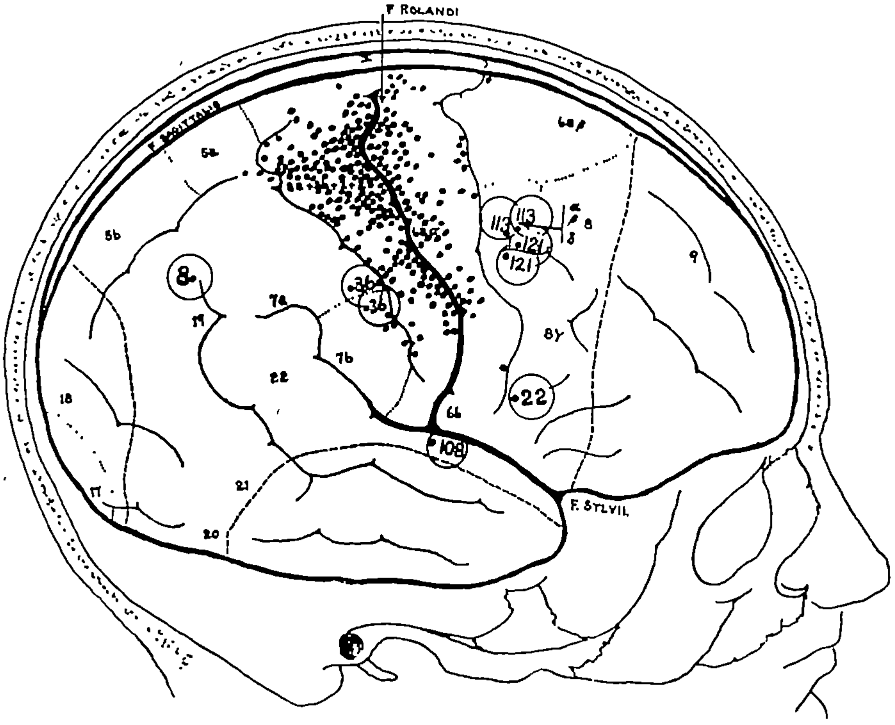


FIG. 15.—Sensation of hand, arm and shoulder.

It will be noted that the antero-posterior extent of motor response is not as great as that of sensation, recorded in the following paragraphs. The most distant motor points are 1½ and 2 cm. respectively from the Rolandic sulcus. The vertical distribution of points is for 5½ cm. along the central fissure.

(18) SENSATION OF HAND, ARM AND SHOULDER (fig. 15).

There are 279 points on this chart, 91 of these (32 per cent.) lie in front of the fissure of Rolando. Sensation in the hand was present during 36 precentral and 73 postcentral stimulations. No attempt has been made to differentiate between the back and the palm of the hand.

There are 170 points, stimulation of which has resulted in arm sensation. Fifty-five of these points lie in front of the central fissure. The response was localized in the wrist 5 times, in the forearm 20 times, in the elbow 4 times, in the shoulder 15 times. The remaining 126 points were called "arm" sensation. This term has not been exclusively confined to the region between elbow and shoulder.

Most of the sensations have been numbness or tingling. Pain has occurred twice. Sense of movement and desire to move were frequently located in this member. The sensations as such will be discussed later.

Of the atypical points on the chart point 108 on the temporal lobe was checked three times. The operative note made at the time states that it is "unexplained but must be accepted." Point 8 was not repeated but was quite definite. The patient had a tumour of the temporal lobe which may have displaced the cerebral tissue somewhat. In Case 36 an epileptogenic meningo-cerebral cicatrix lay just behind the sensory points indicated. Case 22 was that of a patient whose focus was near the midline in Area 6*a beta*. Points 113 and 121 are unusual only in their grouping together at a fairly distant point.

Attention is again called to the remarkable spread of sensory points anterior to and behind the central fissure.

(19) MOVEMENT OF TRUNK AND LEGS (fig. 16).

The voluntary muscles of the trunk and lower extremity respond only rarely. Doubtless more responses would have been obtained had it been feasible to stimulate the edge of the hemisphere and the mesial surface in the median longitudinal fissure more frequently. The danger of bleeding from sinus and tributary veins makes it unwise to stimulate here unless it is clearly necessary.

Twenty-six precentral points, two of which are on the mesial surface, produced these movements. Twenty-three of the points are for the lower extremity alone. The movements are quite equally divided among the different joints with the exception of the back, for which but one point was found. No motor points for individual toes were found.

In addition there are eight postcentral motor points. Neck movements, but not head turning, are included in this chart, because the neck might be considered "trunk" from a functional standpoint. It is interesting, however, to note that neck movements (5 cases) are found in the vicinity of face movements at the lower end of the Rolandic cortex. This is the same area where certain rare trunk sensations grouped themselves in fig. 17.

The widely displaced points in Cases 62 and 111 are well removed from the epileptic focus of each which seemed to be high up in the precentral region. Similarly in Cases 13 and 38 the patients were epileptics. In the first instance the focus was located at the very uppermost end of the central fissure. The lower end of the fissure was the firing point for the other.

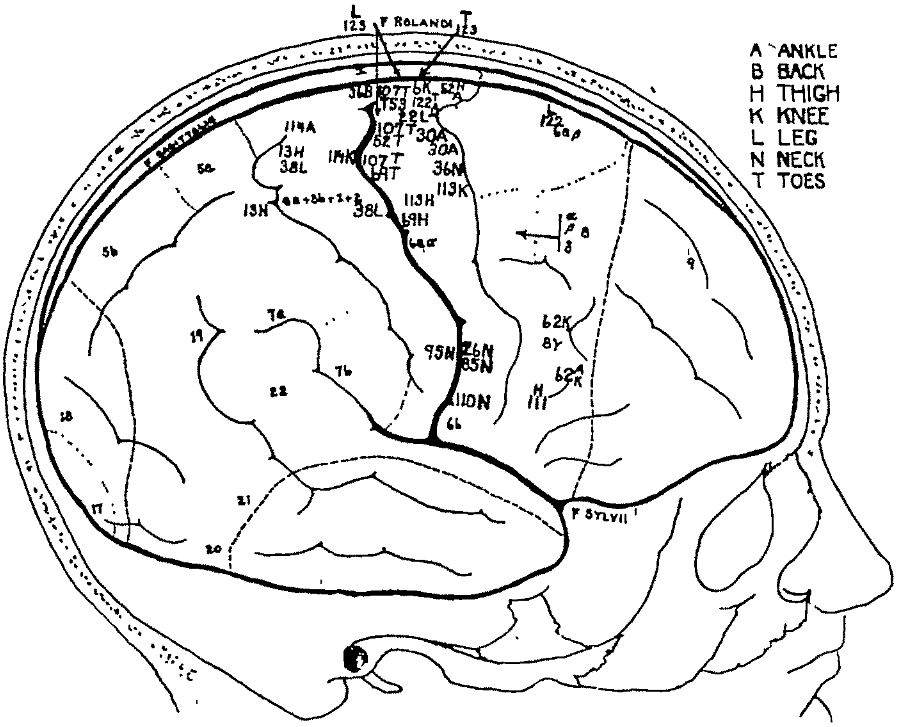


FIG. 16 —Movement of trunk and legs.

(20) SENSATION IN THE TRUNK (fig. 17).

In the main group of response points there are eighteen postcentral and four precentral points. None were reported during stimulation within the longitudinal fissure. The response was often referred accurately to a portion of the trunk which might extend from the opposite axilla to hip. In topographical sequence upon the cerebral cortex the trunk lies below thigh and hip and above shoulder. Epigastric auras in epilepsy will be discussed below but are not included here.

Curiously enough sensation was very rare in the lower sacral and genital regions. This fact may have resulted from the comparatively small number of stimulations within the central fissure, or possibly to a false sense of modesty. Sensation has been produced, however, in the contralateral side of the penis but no motor response. A second group of trunk sensation responses is to be found at the lower end of the fissure of Rolando. This recalls the fact that the neck and throat too are represented in this lower area where they lie adjacent to the face, and not above which would adjoin the principal trunk area.

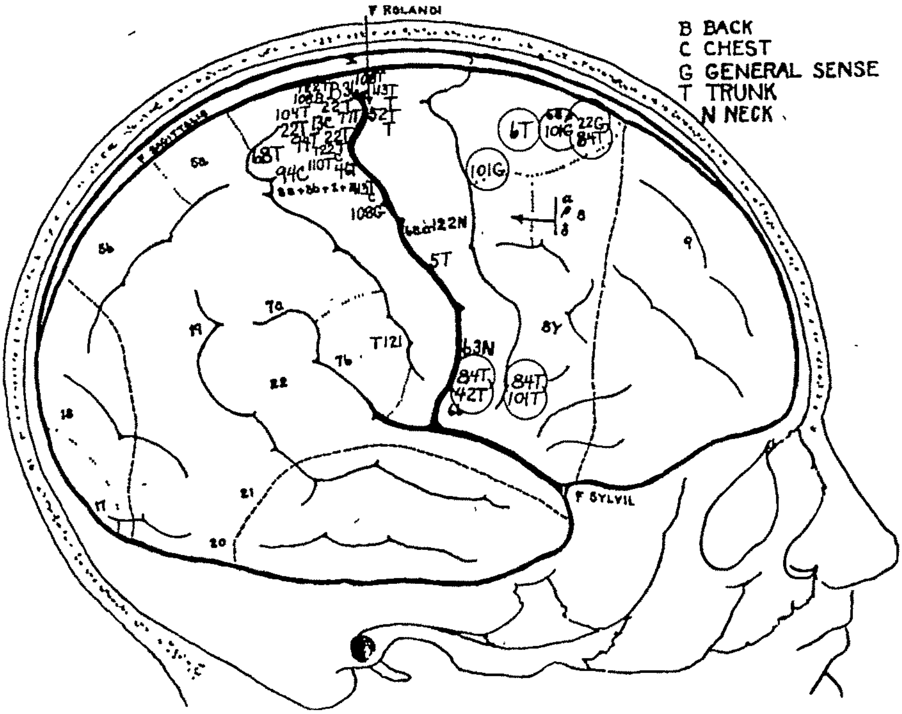


FIG. 17.—Sensation in trunk.

Of this lower group Case 84 was that of a continuing post-epileptic hemiplegia in which sensory responses were present and more or less normally placed, but motor responses were lacking except mouth movements. In none of these four cases was any trunk sensation elicitable in the principal trunk centre.

The responses from the lower centre were described as "pins and needles" in the contralateral side of the body, except for patient 84 who reported a sudden sense of being "paralysed in the right side." The sensation evidently spread through limbs as well as trunk.

A third group of responses were found to lie anteriorly in Field 6*a beta*. Response 6 produced a feeling of "flush" down the contralateral side of the body. This was repeated with the same result and there was no objective evidence of change of colour in the skin. The patient remarked after the second stimulation: "Sometimes I have that feeling before an attack." The responses 101 G were described as a feeling in the nerves all over and the epileptogenic focus seemed to be here. The sensation in that case was reproduced several times without warning.

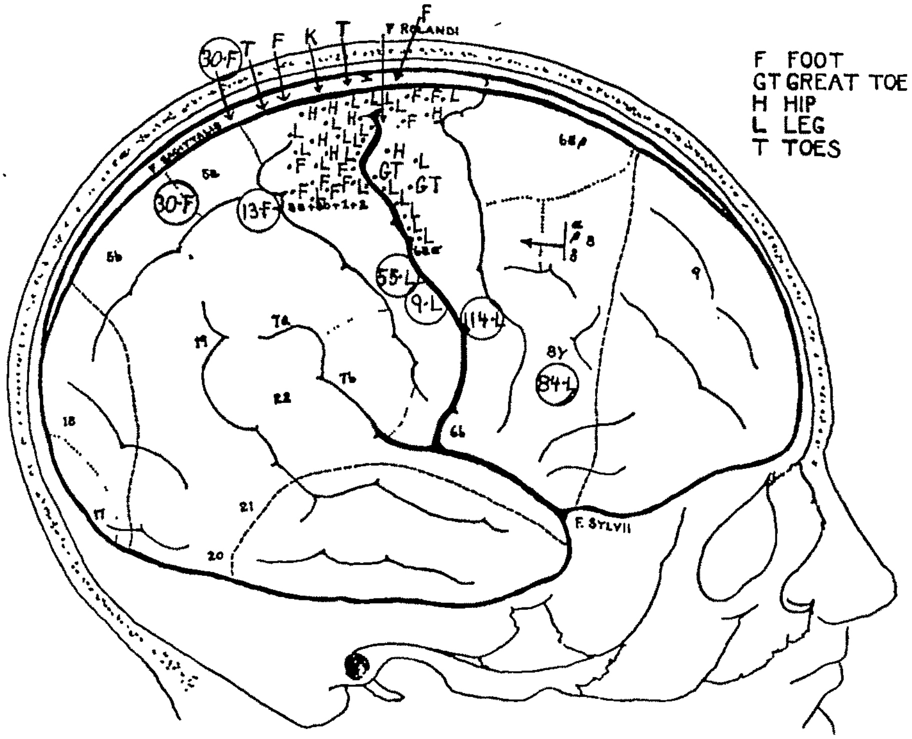


FIG. 18.—Sensation in leg and foot.

The term "general sense" has been used in the chart (fig. 17) when the patient has been aware of some change in his body aside from an epigastric aura but has been unable to localize it exactly. Thus one patient reported a feeling "as if something were moving inside." Three points in Area 6*a beta* and one point in the postcentral convolution elicited this response.

As far as our evidence from stimulation goes this Field 6*a beta* has more to do with bodily sensation than it has with the adversive movements which are discussed below.

(21) SENSATION IN THE LEG AND FOOT (fig. 18).

Sensation is a more frequent response to stimulation than is movement in the lower extremities. There were 16 precentral and 33 postcentral sensory points, 1 precentral and 5 postcentral of which were on the mesial surface in the longitudinal fissure. In addition to tingling and numbness, sense of movement was reported once, desire to move once (114 H), and once a painful sensation. Sensation in the great toe alone accompanied two precentral stimulations. No ipsilateral sensation was described.

One point in Case 30 is seemingly far displaced but the responses were checked carefully. The other points separated from the main group are doubtless examples of epileptic effect, and Case 84 is that of the patient who was operated upon during post-epileptic hemiplegia.

(22) ADVERSIVE TURNING OF HEAD AND EYES (fig. 19).

By adversive movements is meant conjugate deviation of the eyes to the contralateral side and turning of the head to that side. Adversive movements of the eyes alone occurred as a large group of responses in an area which centres roughly in Areas 8 (*alpha, beta, delta*), but it extends back on to the precentral gyrus. It is remarkable that in spite of frequent stimulation the Area 6*a beta* above has not, in our experience, produced adversive movements of head and eyes as recently suggested.

Adversive movements of the head and eyes together occurred only in a few instances. These responses group themselves in the general area of face representation, as though head turning to the opposite side was allied to mouth pulling to that side. During operation the patient's head lies upon a soft ring and it is prevented from very much turning by the towels, but any attempt at turning is evident both to anæsthetist and surgeon. The more likely explanation of the difference between our results and those of Foerster is that we have probably used less intensity of current and that we have eliminated from this study all true epileptic responses.

It is of interest that no downward deviation of the eyes was observed. This may, in part, be due to the fact that the patient's position under the tent makes it likely he would deviate his eyes down to see the observer spontaneously so that no change might be noted.

The deviation of the eyes to the opposite side from the lower point of Case 28 (fig. 19) was reported by the patient to be "towards a light" which he saw as a result of the stimulation. This is of interest in view of the ideas of some of the early investigators on adversive eye movements in animals. However, none other of the patients made a similar observation.

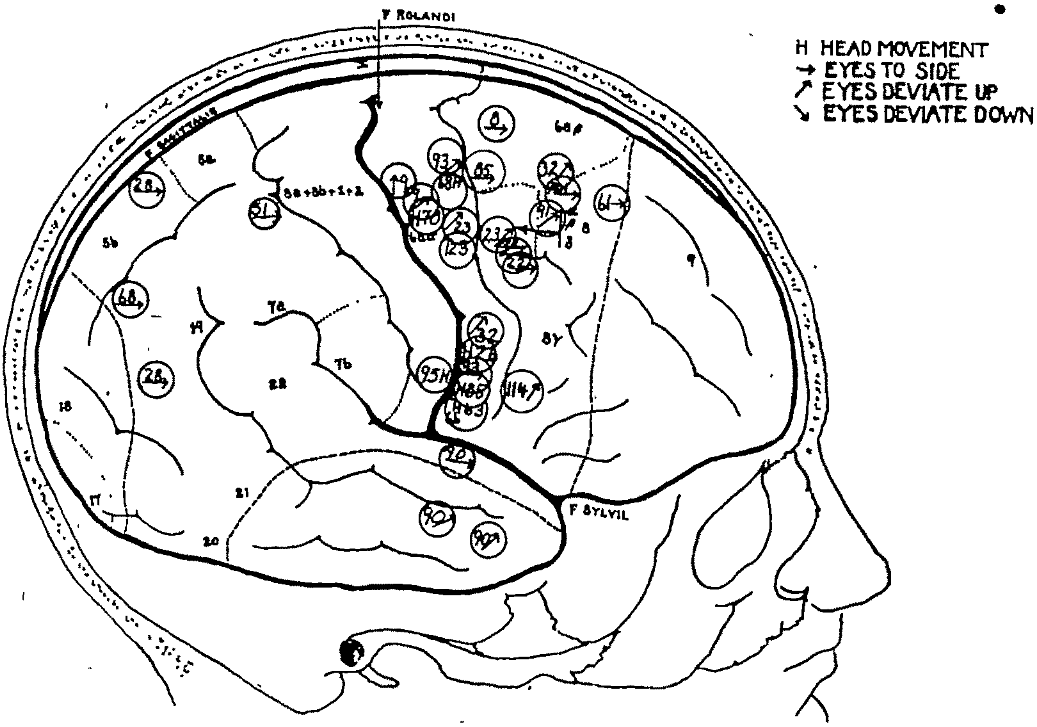


FIG. 19.—Adversive movements of head and eyes.

In Case 90 the unusual location of points for eye-turning led the surgeon to re-examine the responses with no warning before his stimulation, but the response was invariable. In two of the frontal responses the movement was towards the *ipsilateral side* instead of contralateral as in all the others. This might serve to explain turning to the side of the lesion in focal epileptic fits which occurs as a rare exception to the almost universal turning of the head and eyes away from the discharging lesion. The frequency of head and eye-turning in such fits might lead one to expect it to appear more frequently than it has as a result of cortical stimulation.

The frequency of upward deviation of the eyes in epileptic seizures may perhaps be related to the frequency of upward deviation produced by frontal stimulation.

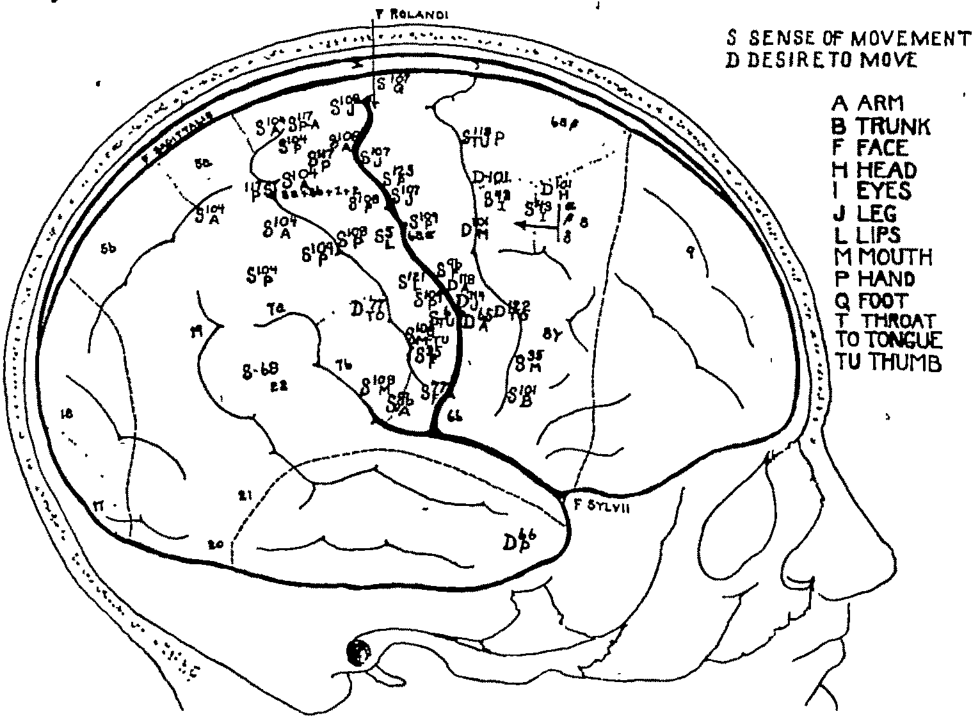


FIG. 20.—Sense of movement and desire to move.

In summary, therefore, there is evidence in this analysis only of a grouping of adversive head-turning responses in the lower Rolandic cortex and there is a larger grouping of conjugate eye deviation responses in the general location of the cytoarchitectural field 8 *alpha, beta, delta* called by the Vogts (1926) the most easily stimulable area for eye movements as the result of their work upon the ringtailed monkey (Meerkatze).

(23) SENSE OF MOVEMENT AND DESIRE TO MOVE (fig. 20).

The sensation of movement in a part was reported by Cushing. We have been somewhat surprised at the frequency of this sensation as it has proved to be the third most frequent description, coming thus after numbness and tingling. The patient realized he had not moved but observed that it felt as though his finger, arm, foot, &c., had moved. When the point (S118 TU P, fig. 20) was stimulated the patient said, "Look at my thumb; it feels as though it were twitching. That's the warning I get." He referred to his habitual aura. There was no observable movement of the thumb.

This response has occurred fifteen times anterior to the fissure of Rolando and twenty-seven times posterior to it. In general the points fall within the same zones as other forms of sensation (*see* S, in fig. 20), the face lying below and upper and lower extremities above.

The response of desire-to-move is also a definite experience to the patient and, like all other unexpected responses, was usually verified by re-stimulation without warning to the patient. These responses were all in front of the central sulcus except D77, which was a desire to move the tongue. The patient said the tongue did not actually move, but as the mouth was closed this could not be verified objectively. D66 lay upon the temporal lobe in the case of an intelligent young woman who observed that she wanted to move her opposite hand up and down. It was associated with a slight sensation in the abdomen. This abdominal sensation was similar to her habitual epileptic aura and a typical attack was produced by stronger temporal lobe stimulation later on. Nevertheless, as the desire to move the hand was again produced at an adjacent point and could not be produced from stimulation elsewhere, it is included here.

The tendency to localization of the desire-to-move anterior to the precental gyrus is interesting, as it seems to relate this desire for movement to motor rather than to sensory function.

(24) IPSILATERAL AND BILATERAL RESPONSES.

There were no examples of verified isolated ipsilateral sensation. This is true even for face and tongue.

There were no motor responses of the ipsilateral extremities and none of the face, except where the movement was part of a bilateral grimace. There was one exception to this last statement, and that was in the case of a little girl who had a focal traumatic lesion just anterior to the Rolandic face area. This produced marked epileptic spread of response and an ipsilateral face movement that was verified repeatedly.

Bilateral motor responses in the extremities are also completely lacking. Bilateral sensation has occurred only rarely, as mentioned above, when a sudden generalized feeling throughout the whole body was produced from Area 6*a beta* (101, fig. 17). Bilateral sensations do occur in the face and in the tongue and bilateral movement in the face, tongue and jaw. Three times patients have reported sensation in both eyes. Once the description was "both eyes like paralysed." The other two had a sensation of lifting the eyes when the eyes did not actually move.

(25) AUTONOMIC RESPONSES.

Pupillary change could not always be watched for. In one case both contraction and dilatation of the pupil was produced at different points by frontal lobe stimulation. Alteration in pulse was observed only once when stimulation of the right frontal pole caused the pulse-rate to double. Repetition of this stimulation, however, caused only a quickening for a few beats.

We have found no valid evidence of a vasomotor centre on the convexity of the cerebral cortex. Once the face flushed as the result of stimulating in the postcentral face area, but it may have been a manifestation of an epileptiform discharge. Perspiration seems to have occurred once as a result of low precentral stimulation.

Salivation occurred in two instances, both from the lower postcentral region, and it accompanied tingling in the tongue once and swallowing the other time.

There is no evidence of gastro-intestinal response to stimulation of the cortex. But in four patients a sensation of nausea was produced. Patient 29 felt nauseated while precentral stimulation was causing vocalization. The other three all had nausea produced by stimulation of the parietal lobe. In each instance it was a familiar aura of an attack. In Case 15 stimulation at two points along the margin of a parietal lobe cyst produced nausea and a little later, when the patient wakened from a natural sleep, he was found to have had a bowel movement. Little importance should be attached to this, however. Vomiting has occurred in one case and was probably incidental.

Epigastric aura.—Sensation in the epigastrium is so frequently an epileptic aura that it was searched for carefully, but was elicited only three times as an aura. In all three cases the localization was in the posterior-superior parietal lobe just behind the postcentral convolution. One patient (Case 24) called it a feeling in the chest, one (Case 94) a rising feeling in the chest and one (Case 20) a weakness in the abdomen. So far as this meagre evidence goes, therefore, the epigastric aura has a localization in the superior parietal lobe posterior to the Rolandic area.

Emotional disturbance.—Weeping has occurred suddenly in two cases only and in both instances the stimulation was high precentral. Laughing occurred only once (Case 110—*see* report above) and then resulted from postcentral stimulation which gave sensation in the lower lip and it was not repeated. It may be said that stimulation of the cortex gives rise to an emotional sensation only very rarely. In fact, there was only one repeated and verified response and in this case weeping was habitual at the onset of a convulsive seizure.

(26) DISCUSSION OF ILLUSTRATIVE CASES.

A number of factors must be considered before these results are compared with data from animal experimentation and anatomical charts. It must be remembered that although we have transferred our results to a standard human chart on which are marked cytoarchitectural fields we do not know what the architectural pattern is in any particular case and how much these boundaries may vary from individual to individual. We have only measured roughly from the central fissure and from the fissure of Sylvius and the sagittal fissure. No greater accuracy can be achieved in any stimulation study.

It has been our routine procedure to begin with the lowest effective stimulation strength and to work up gradually. The central fissure is always outlined by stimulating up and down both sides but sometimes sufficient time was not available for complete mapping. Sometimes the Rolandic cortex proved to be refractory to stimulation except at a few points. The reader may get a truer perception of the meaning of our figures by reviewing the following electrical explorations.

Case 6.—F. W., a boy, intelligent and co-operative, suffering from focal epileptic seizures characterized by a sudden feeling in the right side of body and movements of right hand. Left osteoplastic craniotomy was carried out and excision of a small area of abnormal indurated cortex anterior to precentral gyrus.

Referring to figs. 21 and 22 the results from above down on the post-central gyrus were:—

14. Tingling from the knee down to the right foot, no numbness.
13. Numbness all down the right leg, did not include the foot.
12. Numbness over the wrist, lower border, right side.
11. Numbness in the right shoulder.

3. Numb feeling in hand and forearm up to just above the forearm.
10. Tingling feeling in the fifth or little finger.
9. Tingling in first three fingers.
4. Felt like a shock and numbness in all four fingers but not in the thumb.
8. Felt sensation of movement in the thumb; no evidence of movement could be seen.
7. Same as 8.
5. Numbness in the right side of the tongue.

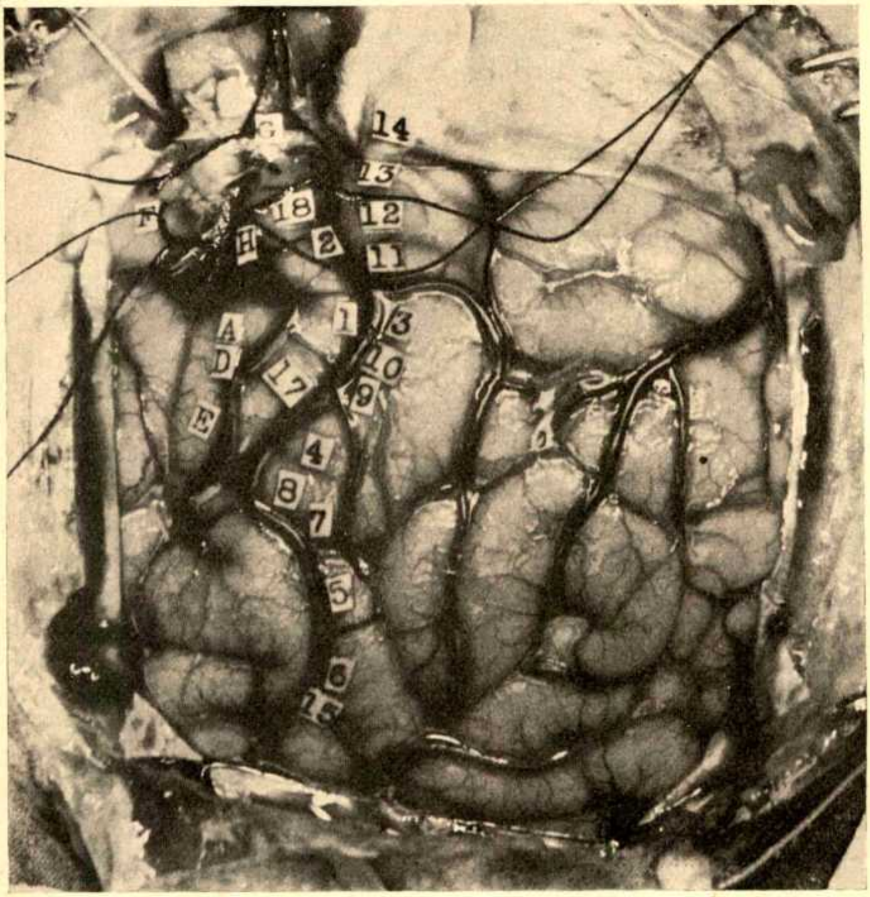
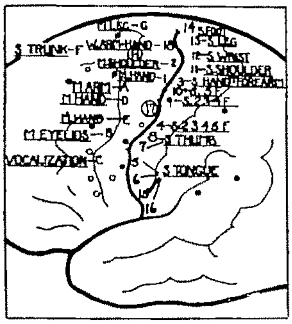


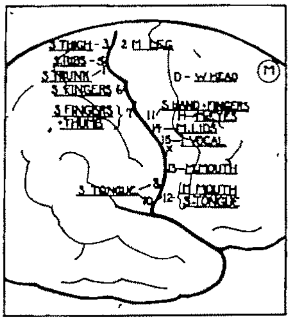
FIG. 21.—Cerebral cortex of Case 6, as photographed at operation. The tickets of reference indicate responses which are described in the text. *See also* fig. 22.

6. Tingling feeling in the right side of the tongue, more at the tip.
15. Tingling in the tongue, associated with up and down vibratory movements.
16. Numbness, back of tongue, mid-line.

Precentral gyrus from above down:—

(G) Flexion of knee.
18. Slight twitching of arm and hand like a shock, and felt as if he wanted to move them.
2. Shrugged shoulders upwards; did not feel like an attack.
(H) Clonic movement of right arm, shoulders, forearm, no movement in trunk.
(A) Extreme flexion of wrist, elbow and hand.
(D) Closure of hand and flexion of his wrist, like an attack.
17. Felt as if he were going to have an attack, flexion of arms and forearms, extension of wrist.
(E) Slight closure of hand; stimulation followed by local flushing of brain; this was repeated with the strength at 24. Flushing was followed by pallor for a few seconds.
(B) Patient states that he could not help closing his right eye but he actually closed both (fig. 22).
(C) Made a little noise; vocalization. This was repeated twice. Patient says he could not help it. It was associated with movement of the upper and lower lips, equal on the two sides (fig. 22).





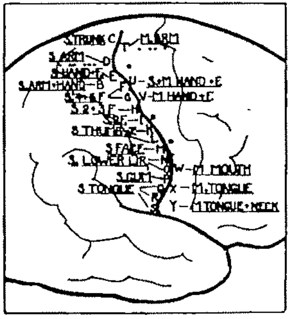


FIG. 22. FIG. 23. FIG. 24.

FIG 22.—Chart of cortical stimulation of Case 6, as prepared at the time of operation. The points are the same as in fig. 21.

FIG. 23.—Chart of cortical stimulation of Case 22, as prepared at operation. The figures and letters indicate localization of points referred to in the text.

FIG. 24.—Chart of cortical stimulation of Case 110, as prepared at operation. The points correspond to those in fig. 4 and the responses are described in the text.

Below C and 17 on the precentral gyrus no responses were obtained even with a strong stimulation, although small attacks had been produced at 17 with a weak stimulus and at H with a stronger one. This refractory condition may be transient but is often encountered at various areas in these cases.

This case illustrated several peculiarities mentioned above, i.e. the desire to move the arm and hand at 18 whereas all other sensory responses were postcentral. The curious sensation as of flushing in the opposite side of the trunk was an aura of his attack and yet sometimes similar sensation has been secured from this area in other cases.

Case 22.—H. T., a woman aged 20, suffering from focal epilepsy originating apparently in the right frontal lobe near 6*a beta*, characterized by: an aura in which "the surroundings seem a little queer" and her thoughts turn to past events. This is followed by loss of consciousness, tonic rotation of eyes and head to the left, twitching of the left face, clonic convulsive movement of left arm and leg, tongue biting and incontinence, in the order given.

Stimulation from above down on the postcentral gyrus with thyratron (bipolar) at 26 gave (fig. 23):—

3. Feeling in leg, "numb," hip to knee left side.
5. Prickly feeling left side of trunk at lower margin of ribs.
1. Numbness left side of body from axilla to crest of hip.
6. Tingling all fingers except thumb.
7. Feeling in all fingers including thumb (no movement).
8. Numb feeling left side of tongue near tip.
10. Same as 8.

On the precentral gyrus:—

2. Tonic movement, left leg, no sensation, "leg moved itself."
11. Tingling left hand and fingers, no movement.
14. Marked closure of both eyes; deviation of left eye to side of stimulation. Other eye not seen.
15. Patient said she was unable to speak and unable to open eyes. No movement.

(X) Convulsive attack not like her habitual ones. It was characterized by clonic movements of mouth, left eye and left face with vocalization.

13. Mouth drawn markedly to left, no feeling in tongue near tip.
12. Mouth drawn to left and feeling left side of tongue near tip.

(D) Peculiar feeling in head; unable to talk for several seconds. Felt as though she wanted to turn her head to the left. No eye movements.

(H) and (G) Eyes deviated markedly upward and to left.

(M) Several small attacks produced from this point and its vicinity during one of which eyes went to left and downward. Once head went to left and once, after stimulation at depth of 2 cm. in brain, the eyes went sharply to left and upwards followed by sharp turning of head to left. Once stimulation near M caused her to say, "felt very peculiar, everything far away, a little bit like before the attacks occur." Sensation in face and lip was elicited but the markers were washed away.

This case illustrates certain points of interest. Sensation in hands and fingers was elicited from the anterior lip of the fissure of Sylvius at 11. At 15 there was inability both to speak and to open eyes. At

D she did not use the word "speak," but said she could not talk. At 12 the same stimulation produced movement of mouth and sensation in the tongue, which means that that point will appear twice on our summary charts, once for each response.

Adversive movements of the eyes were obtained easily at H and G, but no head-turning was obtained until small epileptic seizures were produced. The desire to turn the head was obtained at D and with it a sensation in the head and inability to talk. She used the word "speak" for 15 as mentioned above.

If figs. 22 and 23 are compared the sequence is seen to be the same, but some responses that might be expected are absent in each. No sensory response referred to the trunk was obtained in one, none to the leg in the other, to the face in one or to the throat in either. As is often the case less detail is elicitable from the precentral gyrus. In fig. 22 vocalization is obtained but no response in the lower face or tongue. In fig. 23 vocalization is lacking but mouth and tongue are present.

This variability probably depends upon pre-existing conditions which are not always the same, for we have found, in those cases that were opened up a second time, that different responses were elicitable. The pattern of responses may depend also upon which spots are first stimulated on the day of operation. But the existence of grossly atypical and distant responses argues that in these cases there is a very important role played by abnormal lesions and particularly by the epileptic habit.

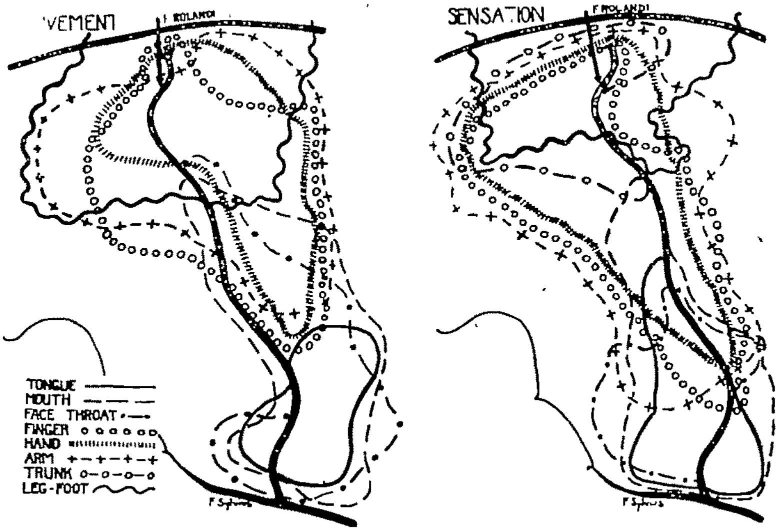
(27) SUMMARY OF LOCALIZATION.

During any one exploration the responses of the sensorimotor cortex vary little, if at all. After stimulation has been carried up and down both sides of the fissure of Rolando and tickets placed upon each positive response, as in fig. 4, the whole process may be repeated with the same intensity of stimulation and the result will usually be identical. The same areas will give no response and the positive points will repeat themselves. But if the same hemisphere be explored at a later operation after a lapse of time, as we have done in five cases, the result may be quite different because areas quite active at the first operation may be mute at the second, and areas which gave no response may later be easily activated.

If a point on the precentral gyrus two-thirds of the distance from the longitudinal fissure to the fissure of Sylvius be stimulated in six different individuals the result will vary greatly so that any standardized chart which localizes the position of those points upon the cortex may be correct for one individual (e.g. figs. 22, 23 and 24) but not for all.

Superimposing all the points of individual cortical charts results in the diagram drawn up in fig. 25. The outlines of finger localization correspond to that of arm and yet in any individual chart (*cf.* figs. 22 and 23) arm will be found above fingers.

As may be seen by reference to this figure (fig. 25) movement has a proportionally larger representation anterior to the central fissure and sensation a larger representation posteriorly, and the two areas, motor and sensory, overlap each other consistently and correspond to each other horizontally.



A. B.

Fig. 25.—Summary of sensory and motor findings in figs. 5 to 20. The lines enclose the areas within which responses were obtained for each subdivision of the body. A. movement. B. sensation.

But in spite of this variability of geographical location illustrated in fig. 25, the sequence of motor and sensory representation from above down is almost invariable. We have expressed the motor sequence in summary form in fig. 26. The list from "toes" above down to "swallow" at the bottom indicates that our conclusions in regard to this sequence is that of the general consensus of opinion with a few additions. The horizontal bar opposite each name indicates proportionally by its length the total number of such responses obtained. The length of the bar to the right of the vertical line shows the number of precentral responses and the length to the left the number of postcentral responses. This illustrates that the hand has responded most frequently, lips next, followed by elbow, wrist, jaw, swallowing and thumb, etc.

Fig. 27 is made up in the same manner for sensory sequence, and here again the hand leads in total number of responses. Tongue now is second in numerical sequence with lips, arm, jaw, face, thumb, and leg following after. Hand and arm sensation have a comparatively large number of precentral responses as well as face and leg, whereas fingers and thumb have relatively few precentral responses.

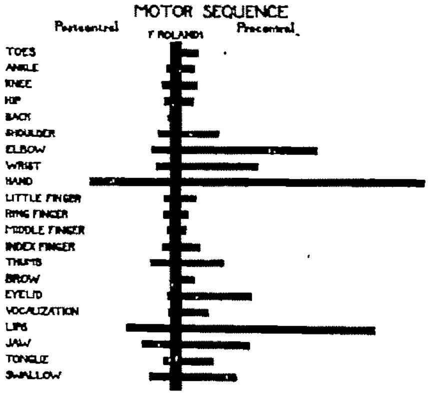


FIG. 26.

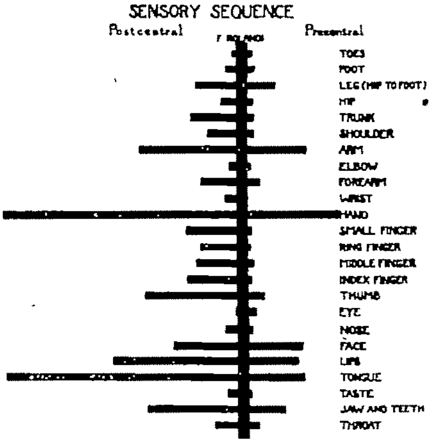


FIG. 27.

FIG. 26.—Motor sequence chart for right hemisphere. The list from "toes" to "swallow" indicates the sequence of motor responses in the Rolandic cortex from the median fissure above to the Sylvian fissure below. The broad vertical line represents the fissure of Rolando. The length of the individual horizontal lines to the right indicates the proportional number of points anterior to central fissure. Their length to the left indicates the number of points posterior to that fissure which gave responses in the part as shown by the names in the column to the left. All face movements are included under the heading of "lips" on this chart. Neck movements have been omitted because of the inconclusive localizing value of the small number of points found. Hand movements in this chart include movements of all of the fingers together.

FIG. 27.—Sensory sequence chart prepared as in fig. 26. Contrary to movement, face sensation is separated from lips. Head sensations have been too scattered to justify their inclusion, and neck sensation points are too few in number.

The sequence relationships may be considered from another point of view illustrated by the homunculus in fig. 28. In figs. 26 and 27 it is seen that toes begin at the top and the members follow in order as though representing a man hung upside down, but that thumb is followed by the head as though the head and neck were erect and not inverted. The larynx represents vocalization, and pharynx swallowing and throat sensation.

The homunculus gives a visual image of the size and sequence of cortical areas, for the size of the parts of this grotesque creature were determined not so much by the number of responses (as for figs. 26 and 27) but by the apparent perpendicular extent of representation of each part when these responses were multiple for the same part.

The large size of the thumb and lips indicates that the vertical extent of Rolandic cortex devoted to those parts in individual cases is very large. Thus the trunk is quite small and the legs and head exceedingly small, while the tongue, which usually occupies a comparatively long strip of the Rolandic lip, is large. The homunculus may be said to be both motor and sensory as the sequence pattern is roughly the same, although there are differences. Comparison of figs.

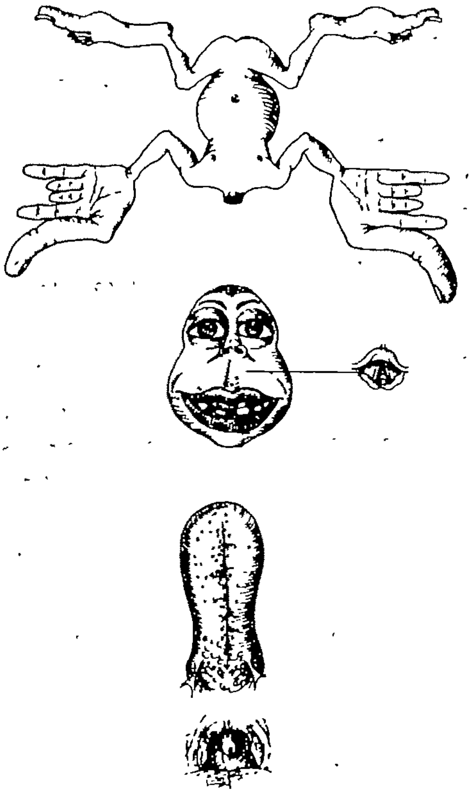


FIG. 28.—Sensory and motor homunculus. This was prepared as a visualization of the order and comparative size of the parts of the body as they appear from above down upon the Rolandic cortex. The larynx represents vocalisation, the pharynx swallowing. The comparatively large size of thumb, lips and tongue indicate that these members occupy comparatively long vertical segments of the Rolandic cortex as shown by measurements in individual cases. Sensation in genitalia and rectum lie above and posterior to the lower extremity but are not figured.

26 and 27 shows that eyelids have a large motor representation. Sensation in the eyes is usually of movement. Eye-turning is not included in the chart. It will be noted, too, that neck is above lips in both sequence charts. The number of responses is as yet too small to be finally certain of the sequence position of neck, of taste and of nose. Foerster places neck between thumb and upper face for both sensation and movement. He likewise places jaw below tongue for both, whereas we would place sensation in teeth and gums below tongue but jaw movement above. Aside from these observations the homunculus represents true sequence. Presumably rectum and genitalia should be placed above feet, that is within the longitudinal fissure, but our evidence is not sufficient for conclusion and they seem to be somewhat posterior to feet.

(28) QUALITY OF CORTICAL SENSATION.

The quality of sensation resulting from cortical stimulation is of interest. In 369 responses the quality was not stated simply because it was the same as in the first or second stimulus which was recorded. In 204 responses it was called tingling or electricity, 131 times numbness, which at times was explained to mean numbness with tingling, at other times absence of all sensation. In 49 responses the patient had a sense of movement when no objective change of position occurred. This applied to a sense of movement of both eyes to sense of movement in one arm, one finger, &c.

There is no localization of quality of sensation, either pre- or postcentral. Eleven times the patient reported a sense of pain in one extremity or peripheral part; it was never severe. Thirteen times a feeling of cold was reported. This last sensation was most frequently applied to the face. As the sense of heat was only mentioned twice it seems possible that tingling was taken for a sense of coldness. A sense of blood rushing was felt ten times. Thickness was the description five times and each time applied to the tongue: swelling once and this also to the tongue.

Desire-to-move, as indicated in fig. 20, has been a definitely reported experience. It is not clear that this is a sensation, but as it was verified by repeated stimulation without resultant movement it becomes an interesting phenomenon, especially as it was anterior to the central fissure in all but one instance. This is to be contrasted with the sense of movement which is chiefly postcentral in location. A feeling of inability to carry out some movement has also been described as though the patient were made aware of stimulation of an inhibitory mechanism. This has most often been described as inability to speak.

(29) CAUSE OF ATYPICAL RESPONSES.

Gross lesions of the brain which deform the hemisphere and displace or alter the Rolandic portion of the brain cause displacement or obliteration of representation. This may explain some of the unexpected results in this report. The lack of anæsthesia doubtless accounts for many differences between human and experimental results, as practically all experimental investigations have been carried out under light ether or barbiturate anæsthesia which gravely alters the reactive state of the cortex. Further, however, it may well be that the human cortex has normally wider associative connections more easily activated.

But what is the significance of a response to electrical stimulation of the cortex? When a motor response is thus produced it is evident that a chain of neurones is activated and an effective impulse passes out to the periphery. When cortical stimulation produces a sensation the mechanism is not at all obvious. It may be that a neurone chain has been activated. If so, whither is the impulse carried? It seems likely that normally the sensory circuit in question is activated by a peripheral stimulus, the resultant impulse of which rises in the central nervous system to a point as high as the postcentral convolution.

Does it stop there or is that point only a way-station on the road to a higher level? It is quite possible that sometimes the stimulation may affect the further course of that sensory pathway toward a higher physiological level. It is also possible and probable that for both motor and sensory responses distant stimulation may activate the primary motor and sensory areas through a connecting neurone chain. These connections are doubtlessly established by pre-existing and sometimes transient conditions.

Sherrington has pointed out the instability of a cortical point. In Case 110 (figs. 4 and 24) above we have shown that a motor response may be moved from the posterior lip of the precentral gyrus to the anterior lip and a sensory response from the anterior lip of the posterior gyrus across that gyrus to its posterior lip by the activating effect of rhythmic repeated advancing stimulation. We have made the same observation in several other cases.

But widespread displacement or extension of function from its usual localization is in these cases most often due to the local or diffuse effect of a lesion which is giving rise to epileptiform seizures, or to the fact that epileptic discharges habitually take place in the cortex even though no objective lesion can be found.

It seems evident that this process may: (*a*) Sensitize or activate areas of cortex; (*b*) may cause widespread displacement of response, and perhaps (*c*) under other circumstances, render normally excitable areas inexcitable to the electrode.

(*a*) *Epileptic activation.*—The epileptic process may sensitize a part of the cortex so that evidence of the nature of neural activity inherent in that part may become evident, although under normal conditions no response to stimulation would be expected.

This applies especially to the parietal and temporal lobes where visual phenomena and even memory processes may be elicited as reported by Penfield (1937). Under such circumstances the repeated epileptic discharge seems to have established a sort of conditioned reflex. A similar effect is seen upon the sensori-motor cortex about the Rolandic fissure in certain cases where an oft-repeated seizure has produced a Jacksonian march. As a result the parts of the Rolandic cortex involved in the habitual march may give a more detailed and finely divided response to electrical stimulation than usual. This we have called epileptic activation.

(*b*) *Spread.*—For example, if an epileptogenic focus be located at some distance from the Rolandic cortex at the level of the arm area stimulation of the arm area gives, as expected, a sudden feeling in the arm. But stimulation of the cortex about the focus and over the intervening cortex produces likewise the same identical sensation in the arm. It is apparent that the whole large area in question has developed the capacity of discharging selectively that one Rolandic response.

This is an evident spread of response due to the influence of an epileptic focus. In a so-called idiopathic case of epilepsy where no objective focus can be demonstrated the same spread may occur.

(*c*) *Inhibition* of response evidently obtains in the cerebral cortex of epileptic patients. It seems likely that in some cases this is due to post-convulsive vascular changes (Penfield, 1933). In others there may be a true post-seizure refractory stage.

(30) DISCUSSION.

After the elimination of instances of widely displaced responses due to epileptic spread and to pathological distortion there remain the great majority of responses to be considered as evidence of localization of function. These are normal responses to be expected from the human cerebral cortex free from any anæsthetic effect.

We find no evidence in favour of the extension of the motor cortex to Areas 6*a beta*, 5 and 22 as described by Foerster (1936A) and illustrated in fig. 3. Somatic motor responses are obtained from the Rolandic cortex, i.e. pre- and postcentral gyrus, but not from other areas of cortex if subconvulsant stimulation be used. Even turning of the head and neck to the opposite side (adversive movement) is not obtained under normal conditions outside of the Rolandic cortex. From the animal experiments of the Vogts we had expected that in man stimulation of Area 6*a beta* would produce head aversion, but so far in our experience and with the technique which we have employed, Area 6*a beta* has not proved to be a "frontal adversive field."

The difference between our conclusions in this regard and those of Foerster may be only a difference of interpretation explained as follows: We have used a minimal intensity of stimulation in the Rolandic zone and have then increased it markedly and even altered its wave frequency to try to produce results in the more distant cortex. But we have not included epileptiform seizures among our responses. On the contrary we have eliminated all convulsive movements, whether tonic or clonic. The criterion of an epileptiform seizure is that the phenomena produced by stimulation continue and may advance after withdrawal of the electrode.

There is great similarity in the mass movements or turning movements which Foerster obtained from the different "extra pyramidal" cortical areas outside the Rolandic cortex, and it seems likely that use of strong faradic currents made it possible to obtain them and that they are in reality evidence of an epileptiform discharge. Adversive movements occur so frequently during such discharges, in various localities as soon as the discharge involves any considerable part of the hemisphere, that it seems probable the mechanism of its production is brought into play by the fit without its being a manifestation of localized cortical function.

As a simple motor response adversive head-turning is produced occasionally from the lower end of the precentral gyrus, while conjugate contralateral deviation of the eyes may be produced by stimulation in the vicinity of Area 8 *alpha, beta, delta* in and just anterior to the precentral gyrus.

Our results indicate that stimulation of the precentral gyrus in a zone next the central fissure most frequently gives rise to motor movements (fig. 29). But with no increase in stimulation strength there are in numerous cases responses from points anywhere over the precentral gyrus. From the postcentral gyrus also, but much less frequently, motor responses may be obtained, especially its anterior lip as shown in fig. 29.

Thus our results from stimulation resemble those of Grünbaum and Sherrington in the chimpanzee except that they got no responses from the postcentral gyrus (*cf.* figs. 1 and 29). This may be due to a difference in man and anthropoid, or more likely it is due to the light anæsthesia which it was necessary for them to use during the stimulation. If in fig. 1 the cytoarchitectural map of Bucy below be compared with the stimulation map of Grünbaum and Sherrington above it is evident that the motor responses occurred in both 4 and 6 with no particular tendency to follow the cytoarchitectural pattern, except to cover about the same extent anterior to the central fissure. In the

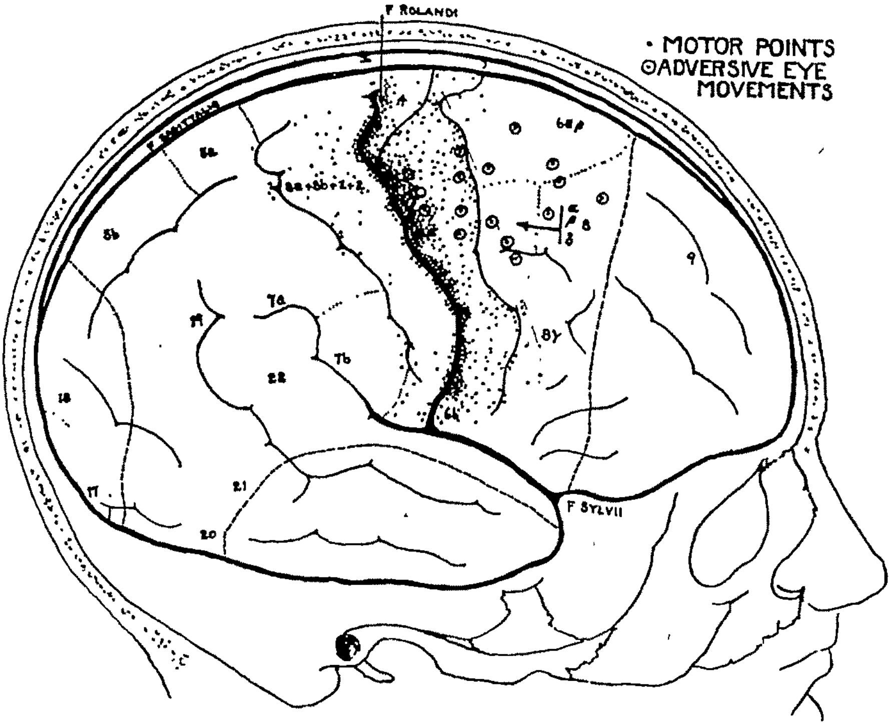


FIG. 29.—Motor cortex. Each black dot represents an actual motor response. The number 4 indicates where Area 4 extends from the anterior wall of the fissure on to the surface, according to Vogt. The remainder of the outer surface of the precentral gyrus is made up of Area 6a *alpha*. ⊙ = conjugate movements of eyes to the opposite side or upward.

same way in fig. 29, where every dot indicates a response, it is shown that close proximity to the fissure on the precentral gyrus renders response most likely without any particular change in those regions where Area 4 spreads out on the surface.

As Area 4 occupies the whole anterior wall of the central fissure this is no doubt the part activated, but Area 6*a alpha* on the precentral gyrus obviously contains neuronal connections with 4, which may often be activated by a minimal stimulus. Such secondary connections must also be possible from the postcentral convolution, especially for movements of hand, arm and shoulder (fig. 14), although these connections are less numerous or less stimulable.

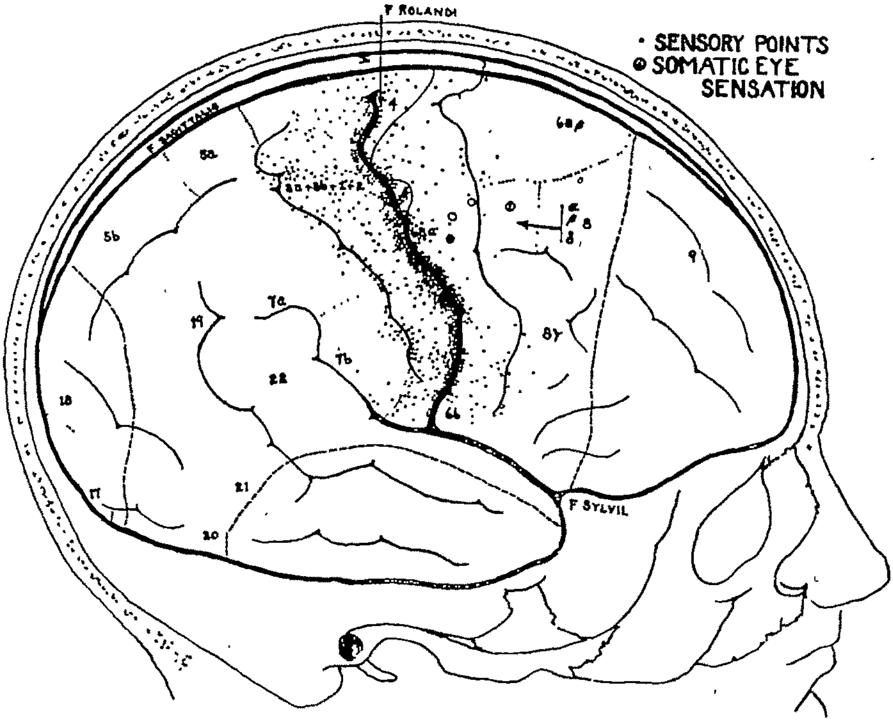


FIG. 30—Sensory cortex. Black dots represent actual sensory responses in some part of the body. ⊙ = sensation in the eyes.

Including these secondary areas the motor cortex, in the broadest sense, should be said to include precentral and postcentral convolutions; that is Areas 4, 6*a alpha*, 3, 1 and 2. But Area 8 *alpha beta delta* probably should be added, as conjugate deviation of the eyes seems to extend forward over this general region as shown by the dotted circles in fig. 29.

Similarly, cortical representation of somatic sensation is found in the postcentral convolution and most often in its anterior lip. But it is also found in Areas 4 and *6a alpha* of the precentral gyrus (fig. 30). Here again it is impossible to tell from stimulation results whether the responses are obtained primarily at one point and secondarily at another. The fact is that the responses were obtained by the same strength of stimulus, usually minimal. The extension of sensation over the precentral gyrus is more frequent than of motor responses over the postcentral gyrus (*cf.* figs. 29 and 30).

These results are in perfect accord with the anatomical work of Poliak (1932) who predicted that sensory representation would prove to be both pre- and postcentral. It also conforms to the theories of Dusser de Barenne (1935, 1936) based upon strychninization of the cerebral cortex. His work suggests clearly that both pre- and postcentral gyri are normally involved in some way in the elaboration of cortical sensation.

It is not infrequent that stimulation produces sensation and movement both in the same part, but never sensation in one and movement in another. So far as our own results go, therefore, it seems appropriate to refer in a broad sense to sensori-motor Rolandic cortex. The invariable consistency of both motor and sensory sequence, however, indicates that within this general area there are two clearly separable anatomical patterns, one sensory and one motor, and that the sensory and motor elements for each part are closely related to each other.

Stimulation along a zone that crosses the precentral and postcentral convolutions roughly at right angles may activate one of the sensory elements as though circuits in both convolutions were normally involved in the registering of sensation. The same is true of the motor representation although it will be seen in figs. 25A and 29 that motor encroachment upon the postcentral gyrus is infrequent in the inferior half of this gyrus except for a small area adjacent to the fissure of Sylvius. The relative frequency of extension of motor and sensory responses across the central fissure for each region of the body may be seen in figs. 26 and 27. Both motor and sensory points seem to be constant for any one individual, but there is great variation in the topographical position of each point from patient to patient.

Ocular sensation, although rare, does exist. It is usually a sense of movement. This might be expected, a priori, when one considers the fact that there is only sense of pain and sense of position in the eye, and sense of pain has little if any representation in the cortex. These ocular sensation responses were few in number but were situated anterior to the central fissure as shown by the dotted circles in fig, 30, corresponding with the conjugate eye movements shown in fig. 29.

Ipsilateral response practically does not exist for motor movements. Only in one case out of 126 explorations did an isolated movement occur and that was of the ipsilateral side of the face. But this was produced from outside the Rolandic cortex and was due to the effect of an epileptogenic lesion. Foerster (1936B) also reported that he never obtained ipsilateral response but stated that Penfield had done so. This must have been a misunderstanding.[1] The same is true for sensation, which is always contralateral, not ipsilateral, even in the tongue and face.

Bilateral sensory responses, however, do occur as epigastic aura and head aura. Bilateral sensation occurs also in face, tongue and eyes. Bilateral movement likewise occurs only in eyes, face, tongue and jaw. This bilateral response is in such striking contrast to its complete absence in the extremities that it must indicate a small degree of true representation of bilateral function in each hemisphere.

Displacement of response by secondary facilitation, which has long been known to be possible for motor points in animals, is also possible for sensory points. Occasional great spread of responses over the cortex due to the influence of an epileptic process and the facilitation sometimes produced by that condition is discussed above but will be taken up at greater length in a subsequent publication.

Vocalization (fig. 11) is a phenomenon with well-circumscribed representation in each precentral gyrus. It is made up of a well-formed loud vowel sound which continues until the patient's breath is exhausted, and indeed he may actually begin again after drawing a breath if the stimulation is continued. It is quite distinct from the grunting which has been previously described and which seems to have its representation at a point lower in the Rolandic cortex and nearer the fissure of Sylvius.

Quality of cortical sensation seems to have no particular localization. Numbness and tingling were the descriptive terms most often used. The frequency (forty-nine responses) of sense-of-movement which was predominantly postcentral is of particular interest in view of the desire-to-move which was precentral in distribution (fig. 20). The fact that only eleven times out of well over 800 responses did the patient use the word pain to describe a cortical sensation, probably indicates that pain has little, if any, true cortical representation. The pain was never severe and never caused the patient to object. The diffuse bodily sensations occasionally produced by stimulation of Area 6*a beta* must await further verification from a larger number of cases. The same is true of epigastric aura which seemed to have a localization in the parietal lobe near the mid-line posterior to the postcentral gyrus.

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[1] This misunderstanding may have resulted from informal conversations with my friend Professor Foerster. At all events I can now corroborate his finding in this regard completely.—W.P.

The responses of the cerebral cortex to punctate stimulation are crude. The movements are never dexterous and the sensations are simple, like elements in a Jacksonian march. But however much these responses may caricature true physiological function they nevertheless give insight into the rôle which the sensori-motor cortex must play in the process of integration. And these human records have certain advantages over experimental evidence, for an animal cannot speak and must be anæsthetized, while a patient usually shows a keen, and often impersonal, interest in the activity of his own cerebral cortex.

BIBLIOGRAPHY.

BARTHOLOW, ROBERTS. (1874.) "Experimental Investigations into the Functions of the Human Brain," *Amer. Journ. Med. Sci.*, **67**, 305 (April).

BEEVOR, C. E., and HORSLEY, V. (1890A.) "An Experimental Investigation into the Arrangement of the Excitable Fibres of the Internal Capsule of the Bonnet Monkey (*Macacus Sinicus*)," *Philos. Trans. Roy. Soc. Lond.*, **181**B, 49.

Idem. (1890B.) "A Record of the Results obtained by Electrical Excitation of the So-called Motor Cortex and Internal Capsule in an Orang-outang (*Simia Satyrus*)," *ibid.*, **181**B, 129.

BIDWELL, L. A., and SHERRINGTON, C. S. (1893.) "Focal Epilepsy, Trephining and Removal of Small Hæmorrhagic Focus: No improvement; Removal of Part of Leg Centre after Electrical Stimulation: Improvement," *Brit. Med. Journ.*, **2**, 988.

BROCA, P. (1861.) "Sur la siège de la faculté du langage articulé," *Bull. de la Soc. anatomique de Paris*, 2 Serie, **6**, 355.

BROWN, T. GRAHAM. (1915A.) "Studies in the Physiology of the Nervous System XXII. On the Phenomenon of Facilitation. (1) Its Occurrence in Reactions Induced by Stimulation of the 'Motor' Cortex of the Cerebrum in Monkeys," *Quart. Journ. Exper. Physiol*, **9**, 81.

Idem. (1915B.) "Studies in the Physiology of the Nervous System XXIII: On the Phenomenon of Facilitation. (2) Its Occurrence in Response to Subliminal Cortical Stimuli in Monkeys," *ibid.*, **9**, 101.

Idem. (1915C.) "Studies in the Physiology of the Nervous System XXIV: On the Phenomenon of Facilitation. (3) 'Secondary Facilitation' and its Location in the Cortical Mechanism itself in Monkeys," *ibid.*, **9**, 117.

Idem. (1915D.) "Studies in the Physiology of the Nervous System XXV: On the Phenomenon of Facilitation. (4) Its Occurrence in the Subcortical Mechanism by the Activation of which Motor Effects are produced on Artificial Stimulation of the 'Motor' Cortex," *ibid.*, **9**, 131.

Idem. (1916A.) "Studies in the Physiology of the Nervous System XXVI: On the Phenomenon of Facilitation. (5) Additional Note on 'Secondary Facilitation' in the Cortical Motor Mechanism in Monkeys," *Ibid.*, **10**, 97.

Idem. (1916B.) "Studies in the Physiology of the Nervous System XXVII: On the Phenomenon of Facilitation. (6) The Motor Activation of Parts of the Cerebral Cortex other than those included in the so-called 'Motor' Areas in Monkeys (Excitation of the Postcentral Gyrus) with a Note on the Theory of Cortical Localization of Function," *Ibid.*, **10**, 103.

Carville, C., et Duret, H. (1875.) "Sur les fonctions des hémispheres cérébraux," *Arch. de Physiologie*, Second Series, **2**, 352.

Cushing, Harvey. (1909.) A Note upon the Faradic Stimulation of the Postcentral Gyrus in Conscious Patients," *Brain*, **32**, 44.

Dana, Charles T. (1888.) "The Cortical Localization of Cutaneous Sensations," *Journ. Nerv. and Ment. Dis.*, **15**, 650

Dusser de Barenne, J. G. (1935) "Central Levels of Sensory Integration," *Arch. Neurol. and Psychiat.*, **34**, 768.

Idem. (1936.) "Physiologie der Grosshirnrinde," Handb. der Neurologie. Bumke und Foerster, Berlin, **2**, 268.

Dupuy, E. (1873.) "Examen de quelques points de la physiologie du cerveau," Paris: Adrien Delahaye.

Ferrier, David. (1876.) "The Functions of the Brain," London: Smith, Elder and Co.

Flourens, M. J P. (1842.) "Rechérches experimental sur les proprietés et les fonctions du system nerveux," 2e Ed., Paris. (Quoted by Ferrier, 1876.)

Foerster, O. (1936A.) "The Motor Cortex in Man in the Light of Hughlings Jackson's Doctrines," *Brain*, **59**, 135.

Idem. (1936B.) "Motorische Felder und Bahnen," Handb. der Neurologie. Bumke und Foerster, Berlin, **6**, 1.

Idem. (1936C.) "Sensible Corticale Felder," Handb. der Neurologie. Bumke und Foerster, Berlin, **6**, 358.

Fritsch, G., und Hitzig, E. (1870). "Ueber die elektrische Erregbarkeit des Grosshirns," *Arch. f. Anat. Physiol. und wissen. Med.* (Reichert und DuBois-Raymond's Archiv), p. 100.

Fulton, J. (1935.) A Note on the Definition of the Motor and Premotor Areas," *Brain*, **58**, 311.

Idem. (1936.) "Somatic and Autonomic Motor Functions of the Cerebral Cortex in Ape and Man," *Proc Inst. Med. Chicago*, **2**, 1.

Grünbaum, A. S. F., and Sherrington, C. S. (1901.) "Observations on Physiology of the Cerebral Cortex of Some of the Higher Apes," *Proc. Roy. Soc. Lond.*, **69**, 206.

Idem. (1903.) "Observations on Physiology of the Cerebral Cortex of Anthropoid Apes," *Ibid.*, **72**, 152.

Hayden, H. S. (1936.) "A New Technique for Surgical Photography in the Operating Room," *The Photographic Journal*, April, pp. 205-209.

Hermann, L. (1875.) "Ueber electrische Reizversuche an der Grosshirnrinde," *Arch. f. d. ges. Physiol. des Menschen und der Thiere*, **10**, 77.

Hitzig, Eduard (1874A.) "Untersuchungen über Das Gehirn," Berlin.

Idem. (1874B.) *Arch. f. Anat. Physiol. und wissen. Med.* (Reichert und Du Bois-Raymond's Archiv), p. 392. (Quoted by Ferrier 1876).

Horsley, V. (1887.) "Remarks on Ten Consecutive Cases of Operations upon the Brain and Cranial Cavity to Illustrate the Details and Safety of the Method Employed," *Brit. Med. Journ.*, **1**, p. 863.

Jackson, J. Hughlings. (1864.) "Loss of Speech." Clinical Lectures and Reports of the London Hospital, **1**, 459.

Keen, W. W. (1888.) "Three Successful Cases of Cerebral Surgery," *Amer. Journ. Med. Sci.*, **96**, 329 and 452.

Lashley, K. (1929.) "Brain Mechanisms and Intelligence," Chicago University Press, Chicago.

Lloyd, J. H., and Deaver, J. B. (1888.) "A Case of Focal Epilepsy Successfully Treated by Trephining and Excision of the Motor Centres," *Amer. Journ. Med. Sci.*, **96**, 477.

Luciani, L., and Tamburini, A. (1879a.) "Ricerche Sperimentali sui Centri Psico-Motori Corticali," *Brain*, **1**, 529 (Digest).

Idem. (1879b.) "Sulle Funzioni del Cervello. Secundo Communicazione: Centri Psico-Sensori Corticali," *ibid.*, **2**, 234 (Digest).

Idem. (1879c.) "Studi Clinici sui Centri Sensori-Corticali," *ibid.*, **2**, 580 (Abstract).

Mott, F. W. (1894.) "The Sensory Motor Functions of the Central Convolutions of the Cerebral Cortex," *Journ. Physiol.*, **15**, 464.

Munk, Hermann. (1890.) Ueber die Functionen der Grosshirnrinde. Gesammelte Mittheilungen mit Anmerkungen," August Hirschwald, Berlin.

Nancrede, Chas. B. (1888.) "Two Successful Cases of Brain Surgery," *Medical News* (Philadelphia), **53**, 584.

Nothnagel, H. (1873.) "Experimentelle Untersuchungen ueber die Functionen des Gehirns," *Arch. f. path. Anat. u. Physiol. u. f. klin. Med.*, **57**, 184.

Parker, R., and Gotch, F. (1893.) "A Case of Focal Epilepsy: Trephining: Electrical Stimulation and Excision of Focus. Primary healing: Improvement," *Brit. Med. Journ.*, **1**, 1101.

Penfield, W. (1933.) "The Evidence for a Cerebral Vascular Mechanism in Epilepsy," *Ann. Int. Med.*, **7**, No. 3, September.

Idem. (1934.) "A Contribution to the Mechanism of Intracranial Pain," *Proc. Assoc. Res. Nerv. Ment. Dis.*, December 15.

Idem. (1936.) "Epilepsy and Surgical Therapy," *Arch. Neurol. and Psych.*, **36**, 449-484.

Idem. (1937.) "The Cerebral Cortex and Consciousness," *Ibid.* To appear shortly.

Poliak, Stephen. (1932.) The Main Afferent Fibre Systems of the Cerebral Cortex in Primates. Berkeley, Cal. Univ. of California Press.

Ransom, W. B. (1892.) "A Case Illustrating Kinæsthesia." *Brain*, **15**, 437.

Sanderson, J. Burdon. (1874.) "Note on the Excitation of the Surface of the Cerebral Hemispheres by Induced Currents," *Proc. Roy. Soc. Lond.*, **22**, 368.

Schiff, M. (1875.) "Untersuchungen über die Motorischen Functionen des Grosshirns," *Arch. f. exper. Path. u. Pharmak*, **3**, 171.

Schmitt, O. H. A., and Schmitt, F. O. (1932.) "A Universal Precision Stimulator," *Science*, New Series, **76**, 328.

Sherrington, C. S. (1893a.) "Note on the Knee-jerk and the Correlation of Action of Antagonistic Muscles," *Proc. Roy. Soc. Lond.*, **52**, 556.

Idem. (1893b.) "Further Note on the Correlation of Action of Antagonistic Muscles," *Ibid.*, **53**, 407.

Thomas, H. M., and Cushing, H. (1908.) "Removal of a Subcortical Cystic Tumor at a Second-stage Operation without Anesthesia," *Journ. Amer. Med. Assoc.*, **50**, 847

Van Valkenburg, C. T. (1914.) "Zur fokalen Lokalisation der Sensibilitat in der Grosshirnrinde des Menschen," *Zeitschr. f. d. g. Neurol. u. Psychiat.*, **24**, 294.

Vogt, C., and O. (1926.) "Die vergleichend-arkitektonische und die vergleichend-reizphysiologische Felderung der Grosshirnrinde unter besonderer Berucksichtigung der Menschlichen," *Naturwissenchaften*, **14** (50), 1191.

COMPRESSION OF THE CHIASMA, OPTIC NERVES, AND OPTIC TRACTS BY INTRACRANIAL ANEURYSMS.

BY GEOFFREY JEFFERSON.

RUPTURE of an intracranial aneurysm has familiarized us with a subject, with a pathology, with a symptom-sign complex which was rapidly fading out of clinical medicine and certainly out of surgery. Time was when aneurysms were a prime differential possibility in any regional surgical diagnosis, and although this is still true, the likelihood of its being the correct interpretation of a clinical problem has become much less during the last fifty years. At the same time our all-round knowledge of aneurysms has considerably advanced and nowhere more than of those within the skull. During the last fifteen years, since indeed the important papers of Beadles, Fearnsides, and notably C. P. Symonds, the neurological world has become so familiarized with the pranks of aneurysmal leakage, and so many important publications have been made upon them, that there might seem to be little reason for traversing so familiar a road. Any such conclusion would be far from the truth, for there are still many blank spaces to be filled. Indeed there is only one outstanding natural experiment of which we can be said to have learned a great deal, and that is the syndrome produced by the sudden effusion of the blood itself into the subarachnoid spaces. But even in this familiar field we still do not know everything. As for the aneurysms themselves, their histological structure, their sites of election and their natural history, we know a good deal and are in process of learning more. It is well established that the pressure exerted by a basal aneurysm may cause paralysis of cranial nerves, amongst others the optic, and the optic pathways. It is with the object of adding something to this side of the picture that the present contribution comes to be made. A search of the literature confirms the fact that amblyopia and field defects are uncommon with aneurysms, for no more than sixty-six cases can be discovered. On the other hand, those here reported for the first time lead to the reflection that the relationship is not quite so uncommon as the figures would indicate. Diagnosis, at one time thought to be beyond human power, has been made easier by certain important aids, such as angiography, and by the discovery of certain cranial alterations observable on the X-ray film, details of which will transpire as the clinical cases are reviewed.

Accepting the clinical classification of Edwin Bramwell, intracranial aneurysms may present themselves as two types: (*a*) the apoplectic; (*b*) the paralytic. It is with the latter only that I shall deal, and of these this paper will be concerned only with such as have affected the visual apparatus in one way or another, that is by compression of the optic tract, chiasma or optic nerve. Reference will be made in passing to certain other of the ocular signs of aneurysmal hæmorrhage —subhyaloid hæmorrhage and certain subjective visual disturbances occasionally met with in these cases. As for the material, I have records of fifty-three intracranial aneurysms which can be arranged in the following categories:—

1.	Pure subarachnoid hæmorrhage—with nothing to indicate the precise site of the aneurysm	16
2.	Aneurysms with paralysis of cranial nerves, usually the 3rd nerve ..	9
3.	Saccular (non-fistulous) aneurysms of the internal carotid in the cavernous sinus	16
4.	Basal aneurysms with affection of the visual pathways	12

The majority of these aneurysms have been verified in one way or another; in a few the diagnosis is presumptive only, for there was no operative or post-mortem control. (It must be recorded that even with contrast angiography it is not always possible to demonstrate an aneurysm which is certainly present.) The series of cases with an aneurysm in the cavernous sinus will be dealt with elsewhere, for these subclinoid sacculations do not commonly affect the visual pathways unless they erode the optic canal or break into the sella turcica. Such of the subclinoid aneurysms as have affected vision are included here.

CHARACTERS OF THE ANEURYSM.

Those cases which fall into the groups (3) and (4) are amongst the most interesting of all, for in these the abnormality of the vessel presents itself clinically as a tumour. In some the suddenness of the onset of symptoms will declare the nature of the lesion, but this is not always the case. In others the growth of an aneurysm has been so slow that it may mimic to a nicety the development of a benign tumour, as indeed it is, save that from the patient's viewpoint a tumour likely to rupture and cause his death in a few seconds can hardly be called entirely "benign." And not only may an aneurysm present a neoplastic syndrome, but it may do worse, and that is, mimic a growth so closely in gross appearance as to tempt the surgeon to interfere with it too far. Clotting is so common in aneurysms that a structure which should sign its nature by its obvious pulsation is often met with at operation as a solid non-pulsatile mass. There are few hospitals but boast some story of disaster befalling a surgical Mandarin when he made what sounds to be the juvenile mistake of incising an aneurysm. Those more familiar with aneurysms will extend their sympathy, for pulsation may have been imperceptible, the tumour apparently solid. Nevertheless the smoothness of the aneurysmal wall and its freedom from fine capsular vessels is generally sufficient safeguard against mistake. Even if it is incised the dark brown clot contained in it should give an immediate clue to its nature. As will be related below one aneurysm in the present series was tentatively incised and three others were needled with informative results and without mishap.

COMPRESSION OF THE VISUAL PATHWAYS.

The most important subdivision of carotid trunk aneurysms is that into two classes, supra- and sub-clinoid. The latter are those arising in the cavernous sinus which, as has been said, rarely cause a disturbance of vision. On the whole the clinical picture of these cases is one of ophthalmoplegia with associated disturbance in the trigeminal field. Such visual difficulty as is experienced is due mainly to loss of accommodation by paralysis of the oculomotor nerve or to diplopia. The supra-clinoid aneurysms spring from the carotid at the origin of the ophthalmic or posterior communicating arteries, or at the final bifurcation of the main trunk. With these lesions visual loss is naturally more common.

The relations of the optic nerve, chiasma, and optic tract to the Circle of Willis require brief review in introducing examples of lesions in this situation. The two systems cross one another in such a way that the anterior end of the Circle of Willis lies superior to the chiasma and the optic nerves, whilst its posterior end lies below it and behind it. The grouping of the vessels about the optic nerves and chiasma is so close that an aneurysm arising in almost any vessel can, after primary impingement on the nearest part of the visual pathway, come to compress more distant parts of it and cause progressive changes in the field pattern. Such alteration is an outstanding feature of the aneurysmal syndrome. Thus arises the fact that the linkage between a visual defect and an aneurysm arising from one in particular of the basal arteries is not so succinct, not so uniform in all examples, as might theoretically have been expected. An aneurysm springing from the carotid soon after it has pierced the dura may compress the optic nerve, or the chiasma, or the optic tract, or combinations of all three. None the less the position of the internal carotid on the outer side of the chiasma is such that monocular blindness or a "junction hemianopia" not only ought to be a common result, but is in fact the most frequent single pattern presented. Binasal hemianopia from indentation of both the outer sides of the junction-angle of the chiasma by atherosclerotic arteries has been thought to be a definite entity. It was well figured in a half-forgotten paper by Elliott Smith and from time to time this pathology has been suggested by later writers. There is also the case of Michel figured by Wildbrand and Saenger, and again by Beadles, of cirsoid carotid trunks indenting the chiasmatic junction, but it is a debatable example.

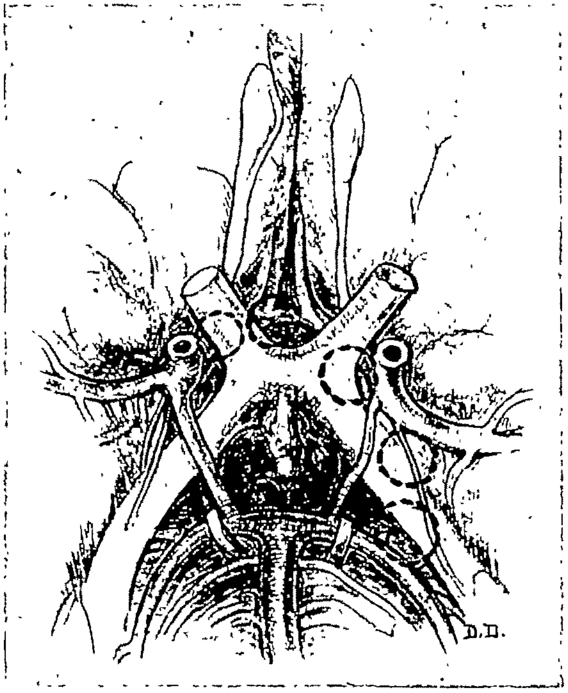

FIG. 1.--Diagram from a normal specimen to illustrate the common sites of aneurysms, and their impingement on the visual apparatus.

As for the optic tract, examination of the recorded cases proves that a pure tract lesion caused by an aneurysm is a rare occurrence. A glance at figs. 1 and 2 will show that the tract could be compressed by an aneurysm arising in any branch of the Circle of Willis except, one would say, the anterior cerebral. Yet a case is on record (Harris [42]) in which an aneurysm of this vessel did in fact reach the tract, and it is likely that it suffers more often than has been supposed, but nearly always in combination with a lesion of the chiasma, or of the chiasma and optic nerves as well.

The cases that form the basis of this communication have been grouped under four headings: (1) Those interfering with the optic radiation and striate cortex, 3 cases; (2) those compressing the optic tract, 1 case; (3) those affecting the optic nerves, 2 cases; and (4) those involving the chiasma, 6 cases. It may well be that in some cases an aneurysm compresses more than one part of the visual pathways, but for clarity of analysis and presentation it seems best to make these subdivisions.

The first group call for a word of explanation. Three cases are presented with homonymous hemianopia sparing the macula and greater or less areas of the contralateral field. The sudden onset of the affection and the non-progressive nature of the clinical pictures leaves no doubt that two are examples of thrombosis of the posterior cerebral artery, the third of thrombosis of some part of the middle cerebral. But in all of these cases the immediate clinical picture had been that of subarachnoid hæmorrhage, and it was not until the days of first anxiety on that score were passed that the visual defect was noted. As this picture has not hitherto been described the cases are presented in full.

GROUP I.—ANEURYSMS INTERFERING WITH THE OPTIC RADIATION AND STRIATE CORTEX.

Case 1.—*Subarachnoid hæmorrhage. Temporary left-sided hemiparesis. Permanent left homonymous hemianopia.*

W. B., male, aged 47, was admitted to the Park Hospital, Davyhulme, on July 26, 1935, on reference from Dr. Higson. He had lost the vision in his left eye in a motor accident two years previously. He had attended an annual legal bowling match, and at 4 p.m. he had felt dizzy and had sudden pain in the head and neck attributed to sunstroke. When seen by his own doctor at 8 p.m. he was groaning with pain over the right eye, and vomiting. There was pronounced rigidity of the neck muscles. During the night he became delirious, and next day presented a divergent strabismus. There was great pain on movement of the neck. He was thereupon sent into hospital under Dr. Morrell Roberts, and a lumbar puncture disclosed a heavily blood-stained fluid. I saw him three weeks later. He was remarkably improved but was still drowsy, and at night inconsequent in his conversation. I found a definite left-sided motor weakness with slight sensory disturbance, and, later, a complete left-sided hemianopia, sparing the macula, in his only seeing eye. The cause of the hemianopia was most probably infarction of the striate area rather than tract compression, for a narrow sector of the superior nasal quadrant was spared, as was an area not more than five degrees in extent around the macula. This is against tract compression, and favours a subsequent thrombosis of the injured vessel. There was no alteration in the optic nerve-head, nor was there ocular palsy. Further lumbar punctures had confirmed the presence of blood diffusely sown in the cerebrospinal fluid. This patient ultimately made a good recovery, the left-sided weakness disappearing though the visual defect remained. In 1936 he had two attacks of minor epilepsy.

The clinical picture was characteristically that of aneurysmal subarachnoid hæmorrhage, but in the absence of anatomical verification the site of the lesion can only be surmised. The oculomotor nerve was not affected in this case. Presumably the aneurysm was small.

Case 2.—*Aneurysmal leakage on two occasions. Recovery. Right homonymous hemianopia. Dyslexia. Later, fits.*

J. E. A., aged 38, male, in September was talking to some friends whilst sitting at the wheel of his car. He suddenly felt a terrific pain in the left temple as if he had been hit. He was able to drive home and put the car away, but felt extremely ill. He managed to get upstairs and remembered no more except that he was violently sick. The next day he awoke to continued pain and very defective vision, as if he had blinkers on, not being able to see anything unless it was straight ahead of him. Two lumbar punctures were done during the next few days and blood found in the cerebrospinal fluid. He resumed work after a month, but his vision was defective to the right. Three months later he had a second attack, which he recognized as identical with the first, but not quite so severe. Spinal punctures were again performed showing a slight staining with blood. The pain was again in the temple and forehead, an acute pain rather than a headache, lasting two or three days. He vomited on this second occasion even more violently than on the first. After the first attack there was a slight suggestion of difficulty in speech, after the second it was pronounced and was associated with dyslexia. Indeed, it seems likely that a good deal of the difficulty in reading of which he complained was due more to an upset of his appreciation of written language than to his visual defect, which proved to be a fairly congruous right homonymous hemianopia which not only spared the macula but some truncated sectors within 25 degrees in the right homonymous fields. Nine months after his recovery of his second attack he began to have generalized epileptic fits, of which there were five over a period of eighteen months, of decreasing severity, led by an aphasic aura. Apart from the hemianopia and a residual dyslexia, he was an entirely healthy man with no pyramidal or sensory abnormality, and able to carry on his business.

In this case it is not certain whether it was the posterior cerebral or a branch or part of the middle cerebral artery which was at fault.

Case 3.—Mrs. H. C., aged 54, referred by Mr. Sumner, of Preston, with a right-sided homonymous congruous hemianopia, dated her symptoms from an attack of "sunstroke" eleven years ago. She had been taking up bulbs in her garden and was suddenly struck by a violent pain in her neck. She was found lying on the path unconscious. She recovered in a few minutes and vomited. She was confined to bed in a darkened room for two weeks, vomiting occasionally, with excruciating pain in the head and back of the neck. She made a very slow recovery and discovered eventually the loss of vision to the right side An interesting more recent feature has been the development of special-sense epilepsy, attacks with a visual aura. She sees extremely bright stars moving in the right field, definitely formed, some two inches in size with points like a formal star figure. They are so bright and dazzling that she can see little whilst they are present, which may be for several minutes. She feels very upset for two or three hours afterwards. In this case the sudden onset of violent occipital and nuchal pain with vomiting leave one with little doubt that the original "stroke" was an aneurysmal leakage from the left posterior cerebral artery followed by thrombosis of the vessel. From my own experience of these cases, it seems that epilepsy is a curiously common sequel of thrombosis of the posterior cerebral artery ("scar epilepsy"). She has a right-sided homonymous hemianopia sparing the macula.

These three cases raise the very interesting point already alluded to—relationship of posterior cerebral arterial thrombosis to aneurysm. It is true that thrombosis sometimes occurs for no discernible reason (e.g. phlebitis migrans), but thrombosis in normal arteries is so rare a happening that it is proper to search for a cause. May it not be that it is sometimes the presence of a congenital defect in the vessel wall, an aneurysm? It is quite certain that aneurysms thrombose and that the territory of their supply becomes endangered by ischæmia. This is a commonplace with aneurysms of the limbs, and no doubt is equally true of the intracranial vessels. In the cases recorded above the visual field pictures suggest infarction of area striata rather than tract compression. Symonds [80] has twice observed compression of the optic radiation by false sacs originating in posterior cerebral aneurysms, and this mechanism is a definite alternative to pure ischæmia. However this may be, the fact of the happening is important and more cases of posterior cerebral thrombosis may in the future be found to be due to this cause.

In the literature homonymous hemianopia of aneurysmal origin has been described seven times (*see* Table of collected cases). In most of this was rather less, but as time passed her oculo motor palsies became more profound on the right side, her face more deeply anæsthetic, whilst a discriminatory sensory loss made its appearance on the left side of the body. The hemiparesis did not materially deepen, and she improved sufficiently to sit out of bed until, on Christmas Eve, she was suddenly seized with violent pain in the head, became unconscious, and died in five hours. At necropsy an aneurysm the size of a pigeon's egg was found arising from the posterior cerebral artery immediately outside the third nerve (*see* fig. 2). It indented the crus cerebri and optic tract and was perfectly placed to produce a full-fledged Weber's syndrome. The mechanism of production of the trigeminal anæsthesia was by compression of the edge of the tentorium overlying the forward passage of the sensory root. The aneurysm had ruptured into the right lateral ventricle through the chorioidal fissure.

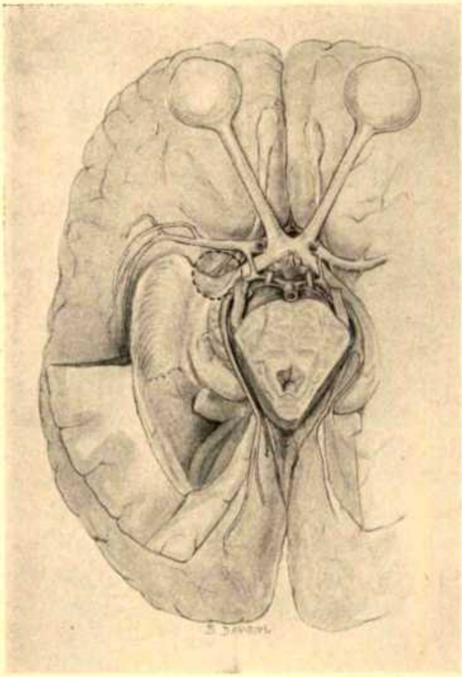

FIG. 2.—Schematic drawing from specimen (Case 4).

Comment.—The vessel most favourably situated to cause a lesion of the optic tract is the posterior communicating, but aneurysms of this artery are generally small and probably they rupture before they have indented it enough to give rise to recognizable visual disturbance. The tract is most often damaged by a blow-out on the internal carotid trunk these cases there was tract compression, as in my own Case 4, or so one presumes. When a hemianopia results from an aneurysm of the carotid trunk rather than the posterior cerebral the field defect must be due to pressure on the tract and not to infarction of the occipital lobe. Only one aneurysm of the posterior cerebral artery of real importance is described in the literature, Byrom Bramwell's Case 3, but it is not included in this paper because no studies of the visual fields had been made, or perhaps, had been possible, for the patient was severely damaged mentally. The visual defect is not mentioned in Squire's case [77].

GROUP 2.—COMPRESSION OF THE OPTIC TRACT.

Case 4.—Aneurysm of right posterior cerebral artery, third nerve palsy, left homonymous hemianopia, left-sided hemiparesis, anæsthesia of right trigeminus.

A. L., aged 29, female, was admitted to Salford Royal Hospital, November 18, 1927. For six months past the patient had felt depressed, headachy and unusually sleepy. Menstruation was not affected. She slept at any time during the day when opportunity presented. During this time she had had frequent visual hallucinations in her left field as of glittering golden buttons which she would try to touch with her hand. Three weeks before admission very severe bitemporal headache suddenly developed, and severe occipital pain. So bad did this become that she was unable to sleep, and she became blind in both eyes for twenty-four hours (probably from hæmorrhage into the sheaths of the optic nerves and subhyaloid exudate). There followed a slow improvement in vision, but she had not been able to see to the left since. Three days after the sudden access of pain the left side of her body became weak, but not paralysed. For the past seven days she had had ptosis of the right upper lid. On admission she was in great pain all over the head, with slight rigidity of the neck. The discs were normal. She presented an incomplete third nerve palsy on the right side with hypæsthesia over the right trigeminal field. There was a complete left homonymous hemianopia with split macula to confrontation, so far as could be accurately judged. She had a left-sided hemiparesis of mild grade with the usual evidences of an organic pyramidal lesion. Lumbar puncture gave a faintly blood-stained fluid with a slightly yellowish background. The diagnosis arrived at was an intracranial aneurysm of the posterior portion of the circle of Willis. It seemed unlikely that anything really useful could be done for her, for it could be by no means certain that the aneurysm sprang from the carotid, hence its ligature would be of very uncertain issue.

An intracranial exploration was done three days after admission because, chiefly, of the intense pain of which she complained. This showed no evidence of bleeding and a decompression was made. Events were to prove than an aneurysm was there, but in a most inaccessible position. Her headache after or the middle cerebral near its origin (*see* figs. 1 and 2). In Gordon Holmes' case, recorded by S. T. Harris, an aneurysm of the anterior cerebral had not only compressed the chiasma but passed back to stretch the right optic tract over it.

COMPRESSION OF THE OPTIC NERVES.

The close relationship between the optic nerve and the internal carotid artery at the anterior clinoid process should be a very cogent reason for unilateral visual loss in carotid aneurysm, and this proves to be the commonest result, judged by the reported cases.

Case 5.—Aneurysm of the internal carotid artery in the anterior end of the left cavernous sinus. Defective vision in the left eye.

M. A., aged 50, female, was admitted to the Salford Royal Hospital, November 14, 1932. She was an emaciated woman who had to give up work twelve months previously because of fatigue and mental instability. However, there were obvious clinical signs suggesting a space-occupying lesion. She feared "an evil spirit moving in her inside" and this she feared would "go to her head." She had been quarrelsome with, and suspicious of, her fellow workers in a large store in which she held a position of trust. It proved impossible to get a connected history from her, but the following facts were established. Five years ago she had experienced paræsthesia of the left side of her face, one year ago it became numb. During the last few months the left eye had slowly closed. She complained of dull left-sided headache. Examination showed a complete left third palsy, pupil mid-dilated, immobile, and the left abducens acting, but not fully. The left disc was paler than the normal

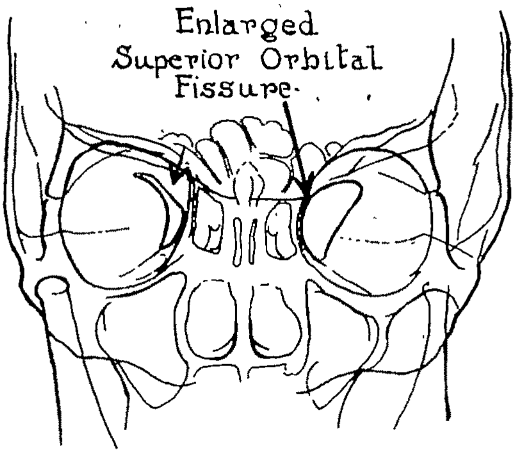

FIG. 8.—Drawing from radiograph (Case 5), showing enlarged superior orbital fissure on side of aneurysm.

right, but was not atrophic. V.A.R. $\frac{6}{6}$, V.A.L. $\frac{6}{60}$. Fields could not be taken owing to poor co-operation, but there seemed to be no significant defect. Anæsthesia was present over the whole left trigeminal field with areflexia cornealis; paralysis of motor branch of left trigeminus. Slight pyramidal signs were present on the right side of the body; abdominal reflexes present but exhaustible on the right, increased tendon reflectivity on the right side, plantars flexor. No impairment of sensation could be established over the body and limbs. There was no bruit on auscultation of the head. X-ray showed enlargement of the sphenoidal fissure on the left side with evident erosion of the greater wing of the sphenoid (*see* fig. 3). In the lateral view Dr. Morris reported a faint large shadow, with definite edges, occupying the floor of the middle fossa on the right side behind the sphenoidal wing. The pituitary fossa was not eroded.

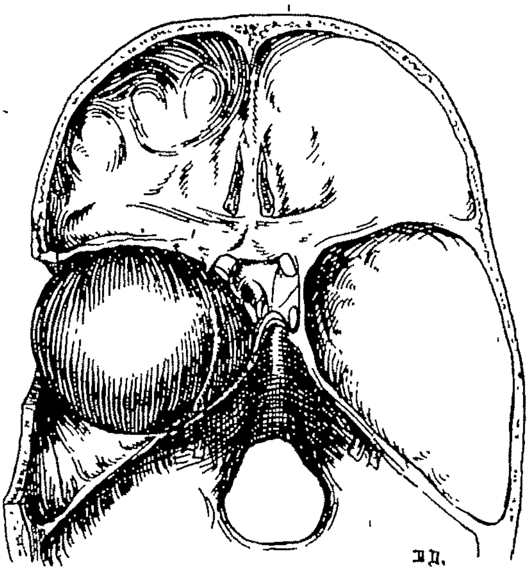

FIG. 4.—Saccular aneurysm of internal carotid filling middle fossa (Case 5).

Comment.—There could be little doubt as to the anatomical situation of the lesion present in this case. The diagnosis was not so certain. Several cases of massive carotid aneurysm had already been studied; in all of them the onset of symptoms had been abrupt. In this case there was a five-year history of an affection of the whole trigeminal field, followed later by unilateral oculomotor palsies, a group of signs so characteristic of aneurysm that this diagnosis was reached. The shadow seen in the X-ray was also in favour of this entity, though it was unlike the common shell-like aneurysmal picture. It was evidently a variant of the more ordinary capsular type of calcification that gives the ring shadow recorded by many people, amongst others Albl.

Operation was undertaken to verify the lesion. On December 28, 1932, a small osteoplastic flap was cut under local anæsthesia in the left temporal region, cutting the edges straight so as to get it to break low down (Lambert Rogers). Dura very tense. Intravenous hypertonic saline was injected at the ankle. The dura was opened and found adherent to underlying cortex. The Sylvian fissure was considerably elevated. Beneath a thin shell of temporal cortex a resistant mass could be detected, at first suggesting a meningioma. It was exposed by excising a small portion of the second and third temporal gyri. The wall was smooth and greyish, entirely devoid of vessels. Palpation revealed it to be pulpy and of very considerable dimensions though its full extent could not be determined without damaging the brain. A sharp needle was inserted into the tumour; dirty brown fluid was at first obtained, but at a depth of 4 cm. bright arterial blood filled the syringe. On withdrawing the needle a high but very narrow stream of bright arterial blood issued from the puncture hole. This was at once controlled by placement of a hot moist pledget of cotton on to the puncture and leaving it undisturbed for ten minutes. Bleeding was then found to be completely arrested and the flap was replaced.

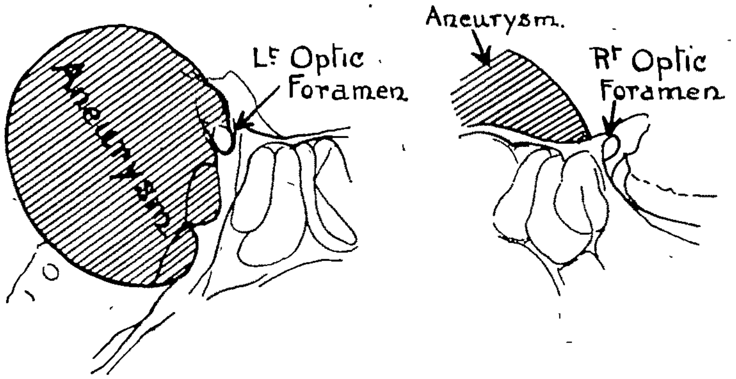

FIG. 5.—Elevation of optic canal by aneurysm (Case 5).

The operation was well borne but the right-sided weakness became progressively more marked and she died thirty-five days after exploration. A huge aneurysm, almost completely thrombosed, was found lying in the whole of the left middle fossa from the wing of the sphenoid anteriorly to the petrous bone behind (fig. 4). It had destroyed the left temporal lobe, only a shell remaining. The aneurysm arose from the intra-cavernous portion of the left internal carotid artery and had compressed the ipsilateral Gasserian ganglion and all the left oculo motor nerves. It eroded into the air sinuses anteriorly. Studies of the optic foramina in this case were made for me at a later date by

Dr. Twining. They show an alteration which we have found to be clinically important (fig. 5) and which calls for immediate comment.

The radiographic alterations.—The striking things were the enlargement of the spenoidal (superior orbital) fissure as seen in the antero-posterior view. In addition to this the bridge of bone which passes from the body of the sphenoid to the lesser wing and forms the lower and outer boundary of the optic canal is seen to be thinned. This also is a characteristic aneurysmal sign, and further examples will be shown. The optic canal has in this case been elevated, and it is surprising that with so much change nearby the visual disturbance was not more pronounced. Many observers have been impressed by the preservation of vision in cases where the nerve had looked to be considerably embarrassed by contact with an aneurysm. It was unfortunate that her mental condition precluded more detailed visual studies.

I have one other case with monocular amaurosis, this time of sudden onset.

Case 6.—*Vomiting followed by severe pains in the face and trigeminal anæsthesia. Development of ptosis. Coarse visual hallucinations of light and then blindness.*

M. F., aged 60, female. On October 1, 1930, she was suddenly seized with vomiting, which continued unabated for three days. On October 5 she experienced severe neuralgic pains in the left side of the face in all three divisions: the pain, to use her own expression, swept over her face like waves of liquid fire, and was intense in the eyeball proper. This ceased after forty-eight hours, but left some tingling in the face. During the night a ball of yellow light appeared before the left eye, burning with great intensity, and in the morning the sight was almost gone. Three days later she was found to be completely blind. She had an immature cataract in this eye and a corneal opacity in the other. On October 7 the left eyelid began to droop and in a few hours the eye closed completely. When seen with her family doctor she was found to have a complete left-sided ptosis and opthalmoplegia, no movements of the eyeball were possible. There was fairly dense anæsthesia of the whole left trigeminal area. She was again experiencing shoots of pain, chiefly in the ophthalmic division, sometimes into the mandibular, and into the ear. There was no weakness on the limbs, and mentally she was clear. Glimpses of the retina were obtained and what could be seen was normal. The patient absolutely refused to enter hospital or to have any further investigations carried out. She was lost sight of except that it was learned that she had survived for some weeks at least, and moved to another part of the country.

Comment.—This is an imperfect case in that there is no verification of the lesion. But the history is so strongly suggestive of aneurysm that this diagnosis will be hard to refute. The sudden development of her catastrophies is strongly in favour of a vascular origin. There were no signs indicative of a subarachnoid or intracerebral hæmorrhage, whilst everything can be perfectly well explained by the sudden blowing out of an aneurysm of the internal carotid artery in the cavernous sinus. It must have been large for it damaged the whole of the trigeminus, indicating that it extended well back in the sinus; on the other hand it extended far enough forwards to damage vision. By exactly what mechanism this last effect was produced must remain conjectural, whether by direct compression or by embolism. The former is more likely as blindness occurred before detachable clot formation was probable. The visual hallucination was an interesting point in this case. It had already been noted in two of the present series (Cases 4 and 5) and will be observable again in a later one, where the compression of the optic nerve was confirmed at operation There are six other cases of blindness amongst the collected cases, one of the most authentic being that of Wildbrand and Saenger. In Jonathan Hutchinson, junr.'s case there was hæmorrhage into the retina (and subhyaloid hæmorrhage can, of course, cause temporary blindness) but at post-mortem a large basilar aneurysm was found extending forwards to compress the chiasma. As a rule the aneurysms have arisen from the internal carotid and have injured the chiasma severely.

CHIASMAL COMPRESSION.

Anterior Cerebral Artery Group.

It has already been said that chiasmal compression is produced by abnormality of the anterior rather than the posterior end of the circle of Willis. The vessels best placed to cause a chiasmatic field defect are the anterior cerebrals and their communicating artery. These trunks lie above the chiasma and so close is their relationship that elevation of the chiasma from below by a pituitary adenoma may cause the vessels to cut into the dorsal chiasmal surface and produce a variant of the typical pituitary field defect. It is probable that the loss of the lower nasal quadrant, seen in advanced cases of pituitary enlargement, is generally caused by this vascular addition to the neural embarrassment, and not by pressure from the upper edges of the optic canals. Conversely, an aneurysm arising from the anterior cerebral vessels indents the chiasma from above and nestles into its now concave upper surface. It will lead to a variable picture according to its placement either exactly in the mid-line or eccentrically slightly to one or the other side, when one nerve will suffer more than the other. It is important to recognize that the situation of these particular aneurysms renders them incapable of producing cranial nerve palsies, other than optic or olfactory. This was not true of aneurysms in the posterior portion of the basal circle of arteries. The suprachiasmatic aneurysm is entirely intradural and buries itself in the under surface of the frontal lobes. The only other nerve that it has an opportunity of affecting is the olfactory pair, but they are sufficiently lateral to escape in most cases, so that anosmia is rare. These aneurysms give a difficult clinical picture. They often evolve slowly, and behave like the tumours that they indeed are. It must be added that a very sudden appearance or worsening of symptoms is more common in aneurysmal enlargements than in any other tumour. More characteristic still is the rapid improvement in vision after a sudden, often monocular, depression of acuity, a point well illustrated by the case which follows and even better by Conway's [16].

Case 7.—Aneurysm of the anterior cerebral artery. Supra-chiasmal compression. Operative verification.

E. K., aged 36, female, was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary from Dr. Fergus Ferguson, August 22, 1933, with the diagnosis of chiasmal lesion, probably aneurysmal. For seven months past she had suffered from headaches, to which she had been unaccustomed. At first left-sided they had spread all over her head. She characterized the headache as terrific, constantly there in some form, but blazing up with very violent pain for half an hour or more. Three months ago when the pain was unusually severe, she vomited continuously for five days. For four months past her vision had been failing in the left eye. There were no other complaints except for uncinate attacks, four months ago during one week, when she had intermittent subjective smells of decaying cabbage. There had been no return of it. On examination she was an apparently healthy woman of average build V.A.R. $\frac{6}{6}$, V.A.L. $\frac{6}{18}$. Pallor of left disc, right normal. No anosmia. Visual fields showed a normal right field, in the left there was a paracæcal scotoma drifting towards the macula. Macular vision was somewhat affected, the fixation point fading and coming back during testing, but the peripheral field was normal. The X-ray of the sella showed no change. There were no other signs, no pyramidal or character changes.

Clearly this was not a pituitary tumour, she had too much pain for a chromophobe adenoma. Even with a normal sella she might have had a suprasellar adenoma, but the patient seemed to be too ill for this. A meningioma of tuberculum sellæ was less likely even than an adenoma, for severe headache is rare with them and the history was too short. After having worried over this case for some time, nothing was done, and she was allowed to go home.

Seen in the out-patients two months later, she declared that her pain was even worse than before and that her vision was failing more definitely. The acuity in both eyes had gone down severely, V.A.R. $\frac{6}{24}$, V.A.L. $\frac{6}{18}$. Her fields now showed a suggestive hemianopia in the smaller isopters and to colour (fig. 6). Menstruation continued regular. Diagnosis was coming nearer. She was readmitted to hospital after some delay, in January, and was found to be visually much worse, V.A.R. 0, V.A.L. $\frac{6}{18}$. This was a remarkable change, for her left eye had been her worse, and now vision had gone on the right. The left field was interesting for it presented a lower temporal defect, changing to a hemianopia with a 1 mm. white disc (fig. 7). This strongly suggested a supra-chiasmal lesion. There was no anosmia, no ocular palsies, trigeminal fields normal, corneal sensation perfect. Bilateral optic pallor was now present with normal vessels. No pyramidal signs. X-ray of sella again showed no alteration. Optic canals normal. Cerebrospinal fluid protein, 40 mgm. B.M.R. normal (—6). Blood-urea and blood-sugar, normal. Wassermann reaction negative.

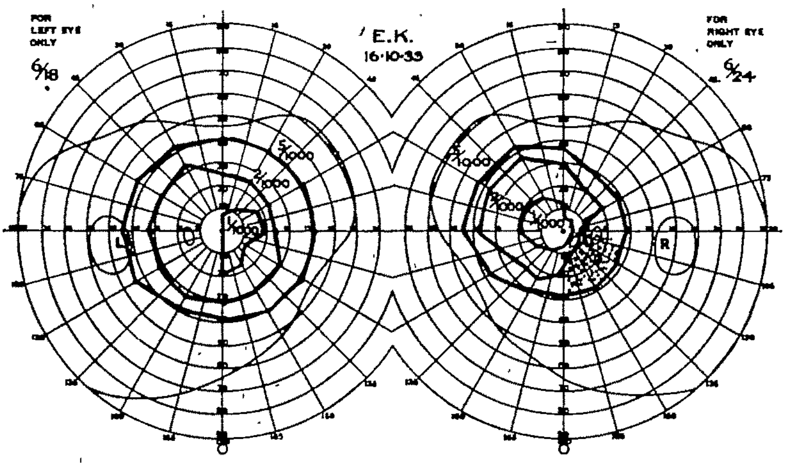

FIG. 6.—Visual fields (Case 6).

Operation.—January 16, 1934, under local anæsthesia, later helped out by ether.

Trotter flap. Uneventful exposure. The dura was elevated without incident and incised along the lesser wing of sphenoid; the pressure was low, moderate amount of fluid. Dissection around the right optic nerves was painful, first referred to the eye and later to the top of the head. The nerve was difficult to bring into view due to a thickened arachnoid. The adhesions were separated and finally a tumour was glimpsed above and to the inner side of the right optic nerve. Gradually, as arachnoid adhesions were divided, a rounded smooth-walled cystic tumour became visible, dark in colour (fig. 8). A little dissection freed it below and the inner side of the left optic nerve was seen and partly cleared. No pulsation was felt. At this point a fine hollow needle was inserted but nothing could be withdrawn, which was surprising as the "tumour" was clearly very soft. An incision 1·25 cm. long was made in the wall of the swelling. There was no escape of contents. A small curette inserted brought out a small quantity of brown material that looked like clot, and in a few moments there was a rush of bright blood that was instantly stopped by wet lintine packing, on the front of what was now clearly a large aneurysmal sac. The material removed was sent to the laboratory and an immediate report returned that microscopically it consisted of old clot. The cotton was left in situ for fifteen minutes undisturbed, and on removing it the field was dry. Muscle grafts were packed on to the front wall of the aneurysm. The wound was closed as usual. Intervention well borne, pulse and pressure

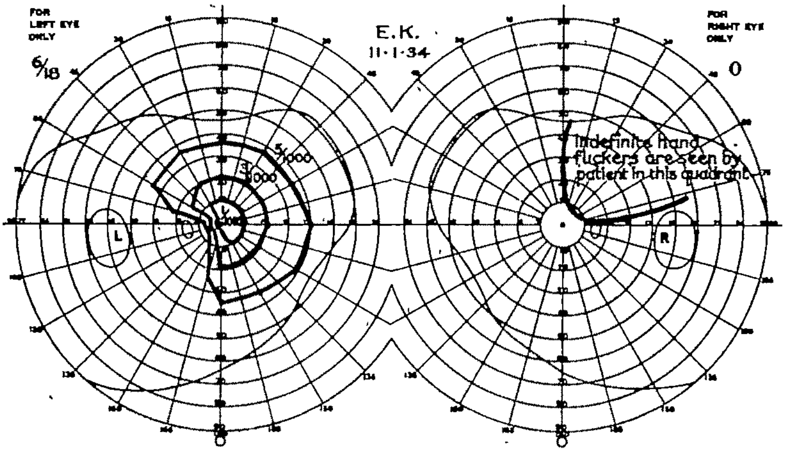

FIG. 7.—Visual fields (Case 6), three months later.

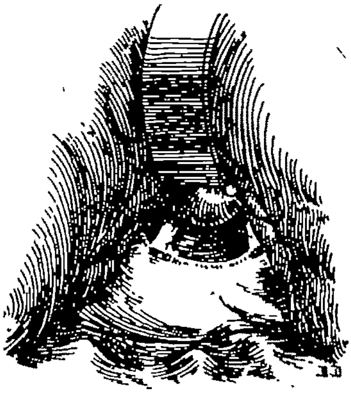

FIG. 8.—Case 6, operation sketch of supra-chiasmal aneurysm.

unaltered. Two weeks after the discovery of the aneurysm bilateral thorotrast injections were made in order to visualize the vessel causing the lesion. Although good pictures were obtained no sign of an aneurysm could be seen. On injection of the left internal carotid she had a temporary attack of aphasia and right-sided paresis which fortunately passed off in ten minutes. The vessel had contracted down on puncture to a narrow cord, and the signs were attributed to severe carotid vasospasm.

Following on this the patient was improved, her headache diminished and there was general physical improvement, possibly because of the mobilization of the aneurysm. She was seen from time to time during the next year. Vision remained unchanged. Eighteen months later she returned home one day from shopping, felt very ill and went upstairs to lie down. Here her husband found her dead when he came home from work. Post-mortem examination discovered an aneurysm of the right anterior cerebral artery at its junction with its communicating branch. It had ruptured into the anterior horn of the ventricle. The aneurysm measured 4 cm. in diameter and was completely thrombosed, except above, where a very thin-walled sac contained fluid blood, and was the site of rupture

Comment.—This case was a particularly valuable one, as we were able to follow the evolution of her chiasmal compression over most of its active course. Beginning with a paracæcal scotoma and depressed acuity in the left eye, the picture changed first to a suggestive bitemporal hemianopia, with a sudden reduction of acuity in the previously better eye, and then to blindness in that eye, with an inferior temporal defect, but improved acuity, on the originally worse side. The relatively rapid evolution of the changes, the extremely severe pain, the normal sella, the circumscription of the lesion, all fitted perfectly with the lesion that was finally discovered embedded on the dorsal surface of the chiasma and optic nerves.

The removal of the aneurysm was a tempting idea but it was decided, and I think correctly, that carotid ligature would be no use, and that control of hæmorrhage during removal would be so uncertain as to make it too hazardous.

Case 8.—Supra-sellar aneurysm. Blind right eye, temporal hemianopia in the left. Calcified shell visible in radiograms. Thorotrast verification. No operation.

E. S., female, aged 49, was admitted to the National Hospital under Dr. Denis Brinton, November, 1935, blind in the right eye and with failing vision in the left. Eight years ago she began to suffer from persistent frontal headache, chiefly right-sided and never very severe. Her vision began to fail in the right eye, first in the temporal field, which went, she felt certain, from below upwards. She consulted specialists but no diagnosis was arrived at, and in the space of two years the eye became blind. Two years later, in July, 1931, vision began to be affected in the left eye, again in the lower temporal quadrant. During the ensuing four years there was a slow advancement to

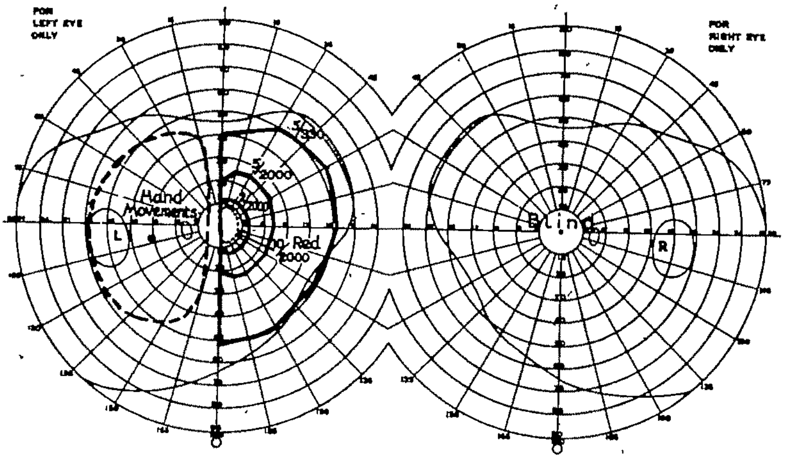

FIG. 9.—Case 8, visual fields.

her present condition. She had had no headache during the last three years. Menstruation, irregular after 45, had ceased after 48. There was no evidence of pituitary dysfunction and no tuberal signs. She was a spare woman, intelligent, interested, concerned lest her left eye should follow the same course

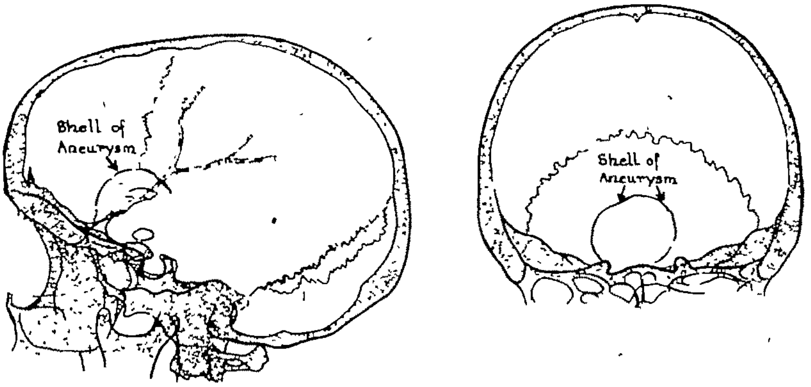

FIG. 10.—Tracing from X-ray films showing calcification of aneurysmal wall (Case 8).

as had the right. No anosmia. There was high grade primary atrophy in the right eye, which was blind. No light reflex. V.A.L. $\frac{6}{18}$, with definite pallor of periphery of disc. There was no external ocular palsies. Corneal sensation normal. Trigeminal fields normal. The left visual field showed a complete temporal hemianopia sparing the macula; hand movements were vaguely perceived in the temporal field (fig. 9).

X-ray.—Sella normal. Above and rather in front of the sella was a fine shell of calcification visible in all views (fig. 10). The upper edge was 5 cm. above the sellar floor; in the antero-posterior view it was 4 cm. wide. It was high above the sella and incomplete. The appearance was highly suggestive of calcification in the wall of the aneurysm. There were no other signs. Serological tests negative.

Comment.—Judged from the patient's own description of the early field losses, it seemed certain that the lesion was suprachiasmatic. At the time of observation the one thing that was sure was that she had a clean-cut temporal defect in her only seeing eye. The shadow above the sella was too high for a calcified Rathke pouch tumour and the sella had not been disturbed by pressure. The likelihood was that this tumour was aneurysmal, and had arisen from the anterial cerebral artery just above its origin from the internal carotid. It had then passed inwards above the chiasma, slowly developing into the large tumour now visible.

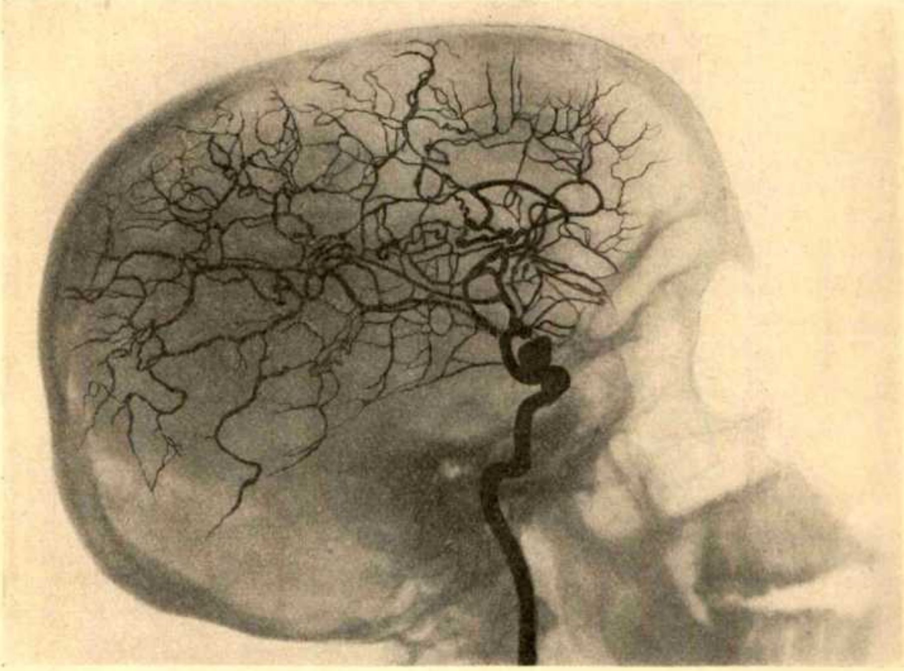

FIG. 11.—Case 8, Angiogram of left carotid aneurysm.

In order, if possible, to make sure of this, angiograms were made.

Operation: November 7, 1935. Bilateral thorotrast injections were made by the writer with Mr. Harvey Jackson. A small tuft of thorotrast could be seen entering the aneurysm from the left side at the origin of the anterior cerebral artery (*see* fig. 11). So small a filling was disappointing considering the size of the aneurysm, but it must be remembered that we are only now beginning to be familiar with the appearance of angiograms of aneurysms in the living. Post-mortem specimens have accustomed us to the fact that aneurysmal sacs are generally more or less filled with laminated clot, and that the amount of blood which they can contain is considerably less than their external size would indicate. There is no doubt whatever that the lesion in this case was aneurysmal. No further operation was performed. Her vision was so precarious that it seemed possible that anything that might be done might make her blind. Even carotid ligature was not quite immune from this risk.

It was curious that although her vision went first in the right eye, that the aneurysm was proved to spring from the left side.

In the next case, though the degree of filling obtained with thorotrast was small, there is little doubt that the lesion is also aneurysmal, for the fields proclaim it in conjunction with the calcification visible in the radiograms, and the notable change in the sphenoidal fissure and optic foramen.

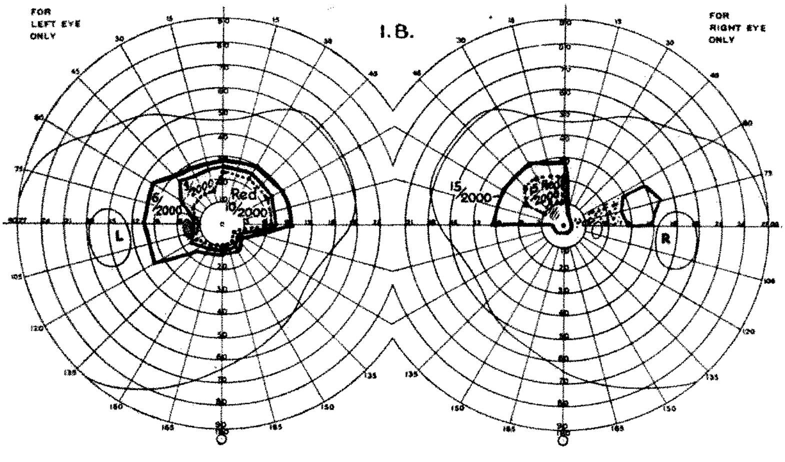

FIG. 12.—Visual fields of Case 9.

Case 9.—I. B., aged 59, male, was referred to the Neuro-Surgical Service, Manchester Royal Infirmary, by Dr. Hamer, of Ashton-under-Lyne.

A previously healthy cotton-spinner (but for hypochromic anæmia two years ago). Six months previously vision in both eyes had decreased suddenly at about 11 a.m. one morning. The interior of the mill looked misty, and objects were not clear. There was no pain, though the eyeballs felt a little sore. The dimness had not increased since he first noticed it, but he had not been able to see clearly enough to allow him to work. He had not been conscious of any pattern in his visual loss, the right eye was much worse than the left. On examination there was nothing remarkable except his general rather yellowish pallor. Blood-count: 3,560,000 erythrocytes, colour-index 0·99, slight aniso- and poikilocytosis, no nucleated red cells. Sugar curve, normal. Metabolic rate, normal (+7). Cerebrospinal fluid, nothing significant, albumin 35 mgm. Bilateral optic atrophy, disc edges well defined, vessels normal. V.A.R. $\frac{1}{60}$, V.A.L. $\frac{6}{24}$. Fields showed an incomplete altitudinal hemianopia in the left, and on the right vision was preserved only in the nasal quadrant and macula, save for a few flickers visible in the upper temporal field (*see* fig. 12).

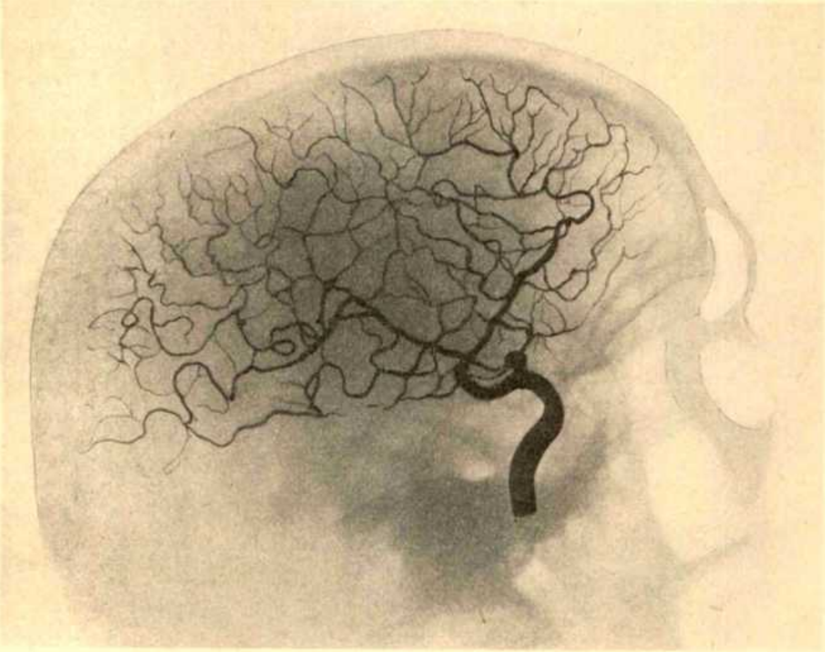

FIG. 13.—Angiogram of Case 9.

X-ray.—A fine line of calcification arose from the sella and curved down again to the tuberculum. The sella itself was completely destroyed posteriorly. Oblique views through the orbits showed an unusual change in the right optic foramen, the lower and outer wall being absent. In addition, the inner end of the sphenoidal fissure was seen to be enlarged, a point in favour of aneurysm, as already well seen in Case 3. These points are, however, subsidiary to other important features in this case. The first is the abruptness of the amblyopia (*cf.* the case of Wildbrand and Saenger), the second is the clearly altitudinal nature of the hemianopia with an inferior defect. Even in the almost blind eye the upper temporal field is clearly scotomatous, flickers being still discerned and a patch of vision is almost chartable. This was not true of the inferior fields of either eye. The lesion is evidently suprachiasmal and nests in the dorsal surface of the chiasma. The aneurysm has probably arisen from one anterior cerebral artery, the right if the more injured nerve is a guide (but see the preceding case). If the aneurysm arises from an anterior cerebral, it is possible that it will not fill with thorotrast (*see* Case 8 above, in which an operatively verified aneurysm failed to do so). Angiograms were made, and show an abnormal tuft of thorotrast approximately at the region of the anterior cerebral artery (fig. 13).

Internal Carotid Group.

In the remaining three cases of this series the chiasmal syndrome was produced by an aneurysm of the internal carotid insinuating itself into the sella in a medial direction.

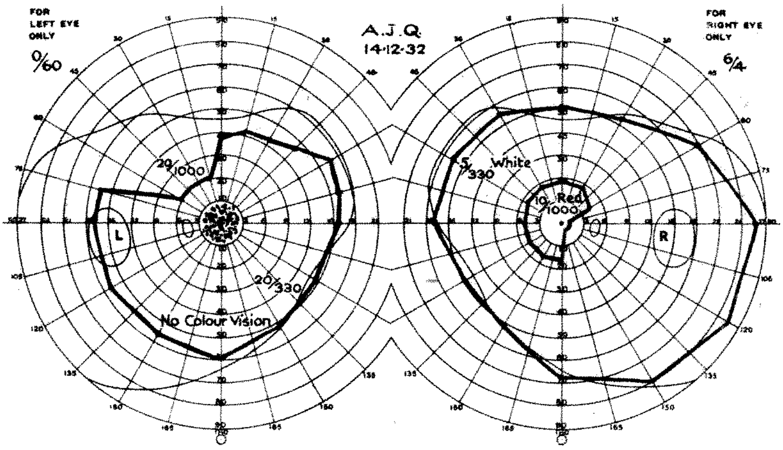

FIG. 14.—Visual fields of Case 10.

Case 10.—*Sudden onset of amblyopia in left eye. Severe headache, partial destruction of sella turcica. Pallor of optic discs.*

A. J. Q., aged 56, female, school mistress, was referred by Dr. Fleming of Liverpool with failing vision in the left eye. For twenty years she had suffered from left-sided periodic headache. Between the ages of 30 and 39 she had nervous breakdowns, in the worst of which her memory forsook her. This was attributed to the strain of teaching. For several years her health had improved. Five months ago, when in bed one night, a bright light glittered suddenly in the left eye and continued for some minutes so that she could not see. Next morning there was internal strabismus in this eye, and it has persisted since; though vision returned, from that day onwards it had slowly deteriorated.

White images floated before this eye, always of the same size and shape. Anything bright on her left side seemed to glitter and sparkle. She has had considerable pain in the left globus oculi and also in the forehead on that side, and again in the cheek below the eye, occasionally in the maxillary teeth, more rarely in the temple. Menstruation ceased six years previously.

On examination.—A very nervous woman of good average physique. She had a radiographically proved gastric ulcer on the lesser curve. There was a left-sided abducens palsy. The left optic nerve head was pale but not atrophic, yet vision was down to finger-counting; V.A.R. $\frac{6}{6}$. Her visual fields showed an upper temporal quadrantic defect in the left eye, where a 20 mm. test object was seen as a small, dull misty dazzle. The right field was full to 5 mm. white, but there was a suggestion of temporal hemianopia to colour (fig. 14). X-ray showed considerable enlargement of the sella, but the type was not very suggestive of pituitary adenoma, there was too much destruction of the dorsum sellæ. All serological tests were negative. Metabolic rate normal (+ 2). No anæsthesia anywhere in the trigeminal field. Diagnosis was by no means easy. The fields were unusual for a pituitary adenoma. Even allowing for compression of the left optic nerve by a nubbin of tumour burst through the capsule, the right field was unusually free from defect, though there was just a suggestion of colour hemianopia. The lesion clearly falls most heavily on the one optic nerve. The dorsum sellæ was broken off and damaged to a degree in excess of expectation, having regard to the short history. Aneurysm seemed to be a possibility, especially in view of the sudden worsening of vision on a night six months ago. That again could have been due to a hæmorrhage into a pituitary tumour, but scarcely with so little change in the field of the right eye. On the whole the eccentricity of the clinical picture favoured aneurysm.

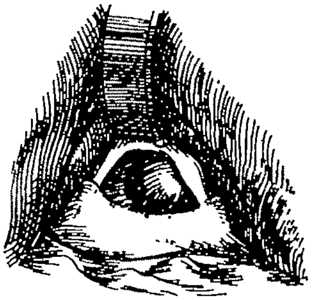

FIG. 15.—Operation sketch of carotid aneurysm, compressing left optic nerve (Case 10).

Operation.—On December 17, 1932, a left-sided frontal flap was turned down (i.e. on the side of the worse vision), and an extradural approach made to the optic nerve. When the nerve was brought into view it was seen to be stretched over a small rounded tumour that projected to its inner side (fig. 15). This swelling did not reach the right optic nerve, nor did it extend far back.

It was dural-clad and clearly was not a pituitary adenoma. There was no sign of pulsation in it; it was dark, and there were no vessels in its capsule. It was decided to aspirate its contents, to discern its nature. A fine long Labat needle was introduced into the tumour. Bright arterial blood was obtained on aspiration. On withdrawing the needle a narrow stream of bright arterial blood spurted from the puncture hole beyond the operation field. Clearly, the tumour was an aneurysm. A pledget of wet cotton placed upon the puncture at once controlled the bleeding, whilst a small muscle graft was cut from the temporalis. This was exchanged for the pledget and held in position for several minutes. The wound was washed out with Ringer's solution and the graft seen to adhere perfectly. The wound was closed. The aneurysm had sprung, in all likelihood, from the last portion of the internal carotid, at the point where it gives off the ophthalmic artery. The problem now arose as to whether to tie the carotid or not. As the aneurysm was well covered with dura it was thought that rupture was not an immediate danger. The problem was left for discussion with the patient, who decided against ligature. Five years later she is still alive and fairly well but for her gastric ulcer. There is no interference with the sight in her right eye. This patient was heard from in October, 1937; she says that there has been no alteration in the vision in her right eye, and that she is fairly well and has no pain.

Comment.—This was a perfect case of unilateral optic nerve compression by an aneurysm. It is possible, but not probable, that her migrainous headaches of many years standing had this lesion as their basis. Severe monocular defect is not uncommon in irregular contoured pituitary adenomas, but I have not yet met with an adenoma in which a more definite field defect has not been present in the other eye at the same time.

Case 11.—*Chiasmal syndrome. Enlarged sella turcica. Alteration in lower and outer rim of optic foramen. Operation. Ligature of internal carotid. Great improvement in vision.*

T. T., aged 23, male, was referred to the Neuro-Surgical Service of the Manchester Royal Infirmary on August 31, 1935, by Mr. Bamford, of Derby, with the diagnosis of chiasmal lesion. Eight months ago he was reading, and by chance discovered that he could not see with his left eye. He consulted Mr. Bamford, who found suggestive defects in the visual fields. Vision in the right eye had failed rapidly and he could only read for two or three minutes at a time owing to blurring of sight. He had had no pain to speak of. There was no other complaint. He was an obese man with a very smooth skin and fine hair, and a physique very suggestive of a chromophobe adenoma. B.M.R. − 11. Neurological examination was negative apart from vision. No disturbance of the autonomic centres. Not impotent.

The visual fields showed a clean-cut bitemporal hemianopia, with the macula just spared (fig. 16). Visual acuity, right $\frac{6}{18}$, left $\frac{1}{60}$.

X-rays of the sella disclosed an elongated sella without much depression of its floor and with the dorsum strongly marked, definitely abnormal, but of an uncommon pattern. The optic foramen in special views caused some comment at the time, for although the right was normal, the left had an exceptional thinning of its lower and outer margin. This is not in itself very uncommon in old-standing pituitary enlargements, according to my own observation, but in this particular case there was an additional peculiarity. There was a definite enlargement of the inner end of the sphenoidal fissure, not, to be sure, of quite the exceptional quality presented in Case 5, but none the less reminiscent of

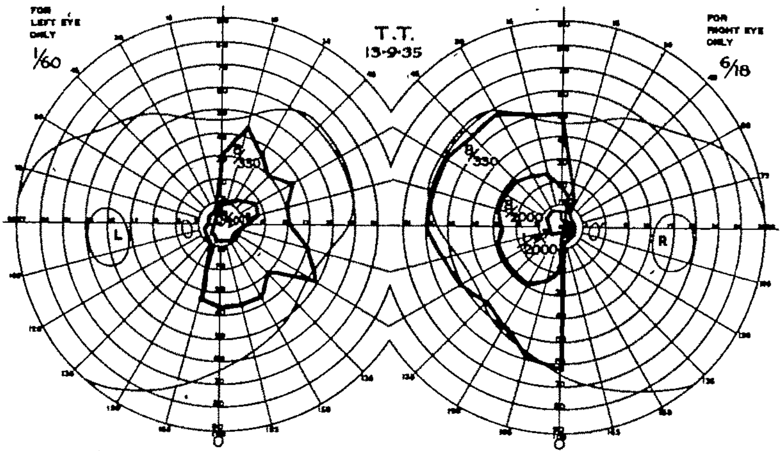

FIG. 16.—Visual fields of Case 11.

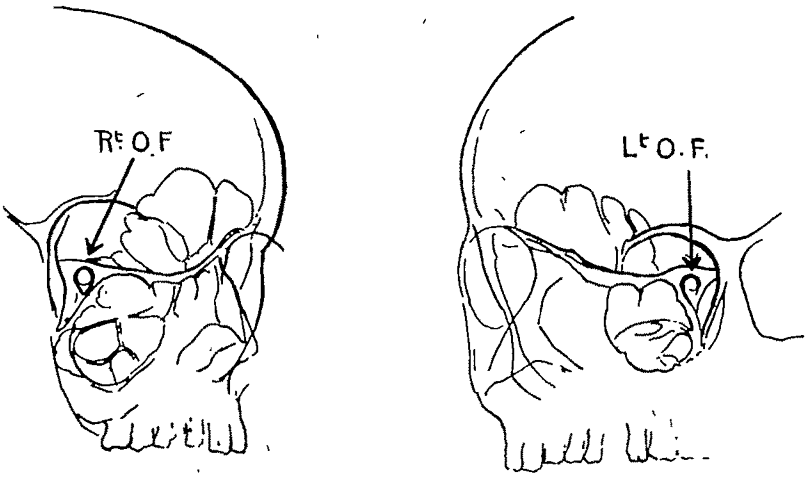

FIG. 17.—Optic foramen (Case 11).

it (fig. 17). This was unusual with a pituitary adenoma, but it was not thought to be definite enough to be completely diagnostic of aneurysm.

Operation.—September 13, 1935. Left frontal osteoplastic flap (the side of worse vision). Extradural elevation of left frontal lobe. When the left optic nerve was brought into view it was seen to be coloured yellow and there was brownish staining in the arachnoid to its inner side. On dissecting the nerve free from its arachnoid covering a brownish tough-walled tumour with contents of putty-like consistence was seen filling the sella, but its anterior edge fell a little short of tuberculum sellæ. The surface of the tumour was curiously opaque, and as a better view was obtained it was seen to pulsate. A finger introduced to verify this fact confirmed strong pulsation in the tumour. It was possible that this was transmitted from the carotid vessels in the cavernous sinus, though this would be unusual, but it was very important to make as sure as possible that the tumour was what it appeared to be, an aneurysm and not an adenoma. A hollow needle was therefore introduced into the tumour and a little blood withdrawn. On removing the needle a smart hæmorrhage occurred, which was quickly arrested. A second puncture further back led to withdrawal of blood easily in the syringe, and the removal of the needle this time was followed by considerable bleeding. Cotton pledgets held in position for a few minutes completely arrested the hæmorrhage; a muscle graft was substituted. It was now as certain as it was possible to be that this was an aneurysm, but there was nothing in its appearance to suggest from which vessel it had come. It was infra-chiasmal and probably represented a blowout from the carotid as it pierced the dura beneath the left optic nerve, the side on which vision had first been affected. The thinning of the lower wall of the left optic foramen in the oblique radiogram of the orbit supported this

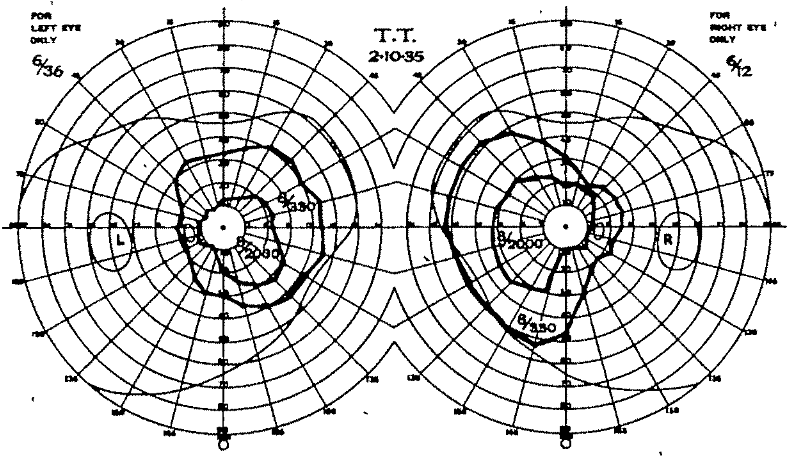

FIG. 18.—Visual fields (Case 11), two and a half weeks after tying left internal carotid artery.

view. He had bled so smartly on puncture that I feared to leave him without ligature. After closing the frontal wound the left internal carotid was tied in the neck. Recovery was uneventful. There was no hint of weakness of the right hand or of aphasia; dynamometer readings ranged around 140 to 160 kilos during the week after operation. There was a very definite and worth-while improvement in vision, following arterial ligation, acuity going up in the left eye from $\frac{1}{60}$ to $\frac{6}{36}$ and in the right from $\frac{6}{18}$ to $\frac{6}{12}$ three weeks afterwards. The improvement in the fields is shown in the charts (fig. 18).

This patient writes in September, 1937, to say that he is very well indeed and cycles ten miles a day to his work.

Comment.—In this case field defects quite indistinguishable from those of pituitary adenoma were present. The history was short, eight months in all, but there was nothing dramatic in the manner of onset. The bodily configuration suggested pituitary dysfunction, hypopituitarism, though the cause might well be pituitary compression from any cause. The sella was curious, it was elongated forwards rather than excavated downwards. The peculiarity of the view of the left optic canal has already been alluded to and especially the opening up of the sphenoidal (superior orbital) fissure.

Case 12.—E. W., female, married, aged 44, was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary, January 13, 1937, complaining of double vision and failing vision in the right eye. She was quite well, apart from unexplained amenorrhœa dating back over eight years, until May, 1936. One morning she awoke with nagging pain over the right forehead. Within forty-eight hours the pain had become very severe indeed, shooting up over the right side of her head and preventing her from sleeping. It continued thus for two weeks and gradually abated, but did not leave her for another month. On the third day of this illness she had diplopia and was admitted to a Sheffield Hospital on this account. It persisted for four months, and since then she has only observed it on looking upwards. She wore an eyeshade over the right eye for four months and on removing it she discovered that vision of the right eye was affected. When reading she found that, with the left eye closed, the print in the temporal field of the right eye was blurred. She was admitted to the Sheffield Royal Infirmary under Dr. Gurney Yates, who found a suggestive bitemporal field defect and made the diagnosis of carotid aneurysm compressing the chiasma. He referred the case to the writer. On examination her build was not remarkable in any way, rather spare, her skin lacking the smoothness and pallor of hypopituitarism. There was right-sided hyposmia, left normal. Pallor of the right optic nerve head, left normal. V.A.R. $\frac{6}{60}$, V.A.L. $\frac{6}{9}$. Visual fields showed an upper temporal quadrantic defect to a 6 mm., a complete hemianopia to a 1 mm., white object on the tangent screen, right eye. The left field showed an upper temporal quadrant only to the 1 mm. white disc, to larger discs the field was full (*see* fig. 19).

There was slight paresis of the left superior rectus, but no other defect of ocular movement could be observed. The right abducens was slightly weak; apparently at one time she had a frank paralysis of this external rectus and wore the eye shade on that account. She was now only troubled by diplopia on looking upwards, left image below right. No anæsthesia of either trigeminal could be detected, though it was carefully searched for on several occasions in view of the distribution of her sudden early pain, so suggestive of aneurysm. Corneal sensation equal and normal. The remaining cranial nerves were normal. No abnormal neurological signs were detected in the arms or legs. Wassermann reaction negative. Cerebrospinal fluid—pressure 80 mm., albumin 35 mgm., globulin normal, cells less than one, Lange curve normal. Basal metabolic rate +1. Sugar tolerance curve normal. X-ray showed an enlarged sella strongly suggestive of an intrinsic pituitary adenoma and without porosis of the clinoids.

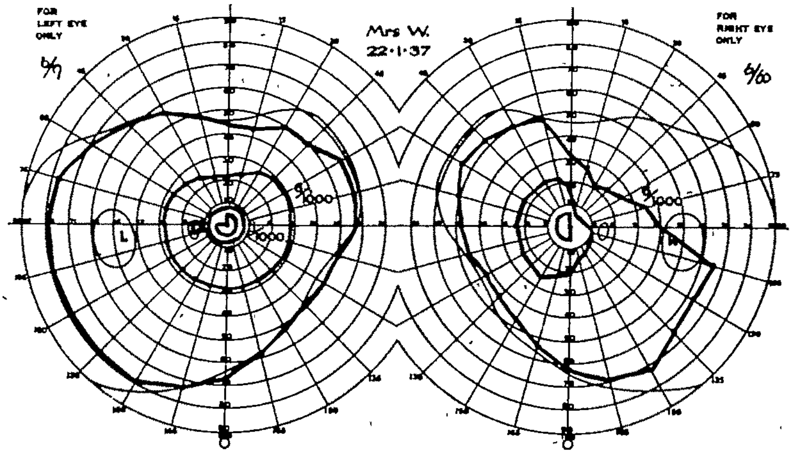

Fig. 19.—Visual fields (Case 12).

In view of the six-year history of amenorrhœa, the bilateral oculomotor disturbance, and the uniform sellar enlargement there was much to be said for a chromophobe adenoma as the cause of her troubles. On the other hand, the suddenness of the onset, the extremely severe pain at its commencement, and the presence of ocular palsies of any kind (though they do occur, if rarely, with pituitary adenoma) spoke for aneurysm. The question was undecided until operation, which proved that Dr. Gurney Yates' diagnosis was correct. On January 26, 1937, a right frontal osteoplastic flap was turned down under avertin and gas anæsthesia. Entrance very difficult owing to exceptional dural adhesions. An intradural approach was made to the right optic nerve. This presented a curious appearance, for it was looped upwards and outwards by a rounded structure, covered with dura, beneath it. Towards the left the diaphragma sellæ, which was not much elevated, sloped away sharply, so that the left nerve was only slightly compressed (fig. 20). A small incision was made into the pituitary diaphragm, which was very thick. No tumour escaped, and cautious examination disclosed an encapsulated mass not much larger than a cherry occupying the right half of the sella. There was no detectable pulsation. A lumbar puncture needle was inserted into the swelling to the inner side of the right optic nerve. Considerable pressure was needed to puncture it, when the needle filled with blood. Several small syringefuls were withdrawn in order to establish the fact that the cavity was truly aneurysmal and was not a blood-filled cyst without communication with a vessel. On removing the needle there was no bleeding but a small piece of temporal muscle was plugged into the opening in the diaphragma for security. Usual closure with a temporary drain. Convalescence proceeded smoothly but for the development of an isolated generalized convulsion on the eighth post-operative day, probably due to œdema, as two anterior parasagittal veins had had to be coagulated. There was no repetition of this fit, and she left the Hospital on the fifteenth post-operative day with her essential condition unchanged.

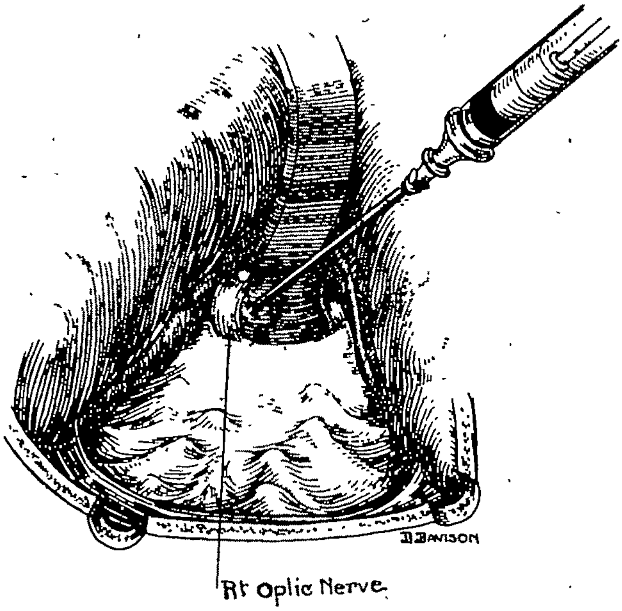

FIG. 20.—Case 12. Operation sketch of aneurysm compressing right optic nerve.

Comment.—The diagnostic problems have already been discussed. It is to be presumed that her amenorrhœa was of pituitary origin. She must have had a small aneurysm compressing the gland for some years prior to the final blow-out. The formation of the larger aneurysmal sac can be very accurately dated to a time only seven months prior to the exposure of the aneurysm. The treatment of this case cannot be said to be completed. She will compress the right carotid for fifteen minutes two or three times daily with the object of inducing thrombosis and opening up a collateral circulation. If the cavity and field restriction in the right eye continue to fail, and especially if there is any further encroachment of the left field, then the right internal carotid must be tied. The aneurysm had been demonstrated to have a thick wall and is covered also by dura so that there is no immediate necessity for ligature. Nine months later this patient continues to be well with no further change in vision.

PREVIOUSLY RECORDED CASES.

I have been able to find records of only sixty-six examples of disturbances of vision by aneurysm in the literature, additional to the twelve just described. They are set out in a synoptic table at the end of this paper. This takes no account, as it might have done, of visual loss, as described by Leslie Paton, from subhyaloid hæmorrhage in diffuse subarachnoid bleeding. But as the mechanism of the production of amblyopia and scotoma formation is quite different in this state from that in the pressure affections of the optic pathways proper, I have omitted my own examples and those of others. It is to be remembered, none the less, as a clinical point, that sudden blindness, or blurring of macular vision, may be due to effused blood in the optic sheaths and diffuse subretinal swelling, rather than to sudden chiasmal compression. The case of J. Hutchinson, Sen., once much quoted, appears to have been of this type, whilst in that of J. Hutchinson, Jun., the same agent may have been effective, but there is also necropsy evidence of chiasmal compression. I have numbered the latter's case amongst those tabulated, but not the former's. In the case of Wildbrand and Saenger, and in that of Van Bogaert, Helsmoortel and Nyssen, the sudden blindness was caused by chiasmal compression, and these cases are naturally included.

Study of the literature brings interesting reflections on the increasing part which retinal and visual-field studies play in diagnosis. The older writers were content to comment to the best of their ability on the sight of their patients, but their accounts are, by modern standards, woefully lacking in precision. Thus it is only during the last quarter of a century that the searcher can find the kind of information which he requires, if he wishes to obtain confirmation elsewhere for personal observation, to reinforce his own findings by similar experience in the hands of others. There must have been important visual disturbances, capable in modern times of informative analysis, in cases which have had to be omitted, by reason of their vagueness, from the analytical table at the end of this paper. Such was Sir Gilbert Blane's case in 1791. This was the first English record of an intracranial aneurysm. His patient was suddenly seized with dimness of vision and suffered from recurrent maniacal attacks for some years. The post-mortem was historic, for it was conducted by John Hunter, Holme and Jenner, who found bilateral aneurysms of the internal carotid trunks an extremely rare condition. Cases are referred to in similar terms by Patterson [61], Bristowe [12], Coe [15], Chevalier [14], Smith [74], Delpech [22], Gull [39], Humble [45], Wood [90], and Timothy Holmes [44]. In a few others, such as Spurgin's [76], Peacock's [62], and Squire's [77], compression of the chiasma or optic tract was noted at necropsy, but no mention is made of clinical tests for vision. Spurgin's case is particularly noteworthy, for, writing in 1825, he describes the case of a man aged 55 who suffered for a short time from fits. He remarks that the patient had cataracts, but could distinguish light from darkness with the right eye. At post-mortem an aneurysm, the size of a hazel nut, of the right anterior cerebral artery was found immediately to the outer side of the olfactory nerve and pressing on the right optic nerve. He removed the right eye and found its dural sheath thickened and distended with blood. This is probably the earliest reference to the presence of blood in the optic sheath in subarachnoid hæmorrhage, and it was made by a country practitioner. An important contribution was made by Lebert [51] in his series of letters to the *Berliner klinische Wochenschrift*, an admirable review of intracranial aneurysms up to 1866. He states that unilateral blindness is a common result of these lesions, but does not discuss the matter in any detail, or furnish any personal observations.

Considering the quantity of the literature on aneurysms, the number of cases relevant to the present discussion is not large, but there have been many disappointments. For example, Beadle's great collection of 555 aneurysmal histories and specimens includes 114 new cases or specimens, but his paper is remarkably free from details of the symptomatology of the aneurysm, although the general effect of his paper is impressive. One case only, that recounted to him by Nettleship, has been gleaned from his remarkable series as having a bearing on the present subject. A good deal of his personal material came from asylums, as did two of Byrom Bramwell's, a vague but important clinical fact. In Fearnside's important paper on aneurysm, his Case 23 had lost the vision in the right eye, but he had had an iridectomy and the eyeball is spoken of as shrunken. At post-mortem the optic nerve was found grey and atrophic, but its precise relation to an aneurysm at the junction of the right anterior cerebral and anterior communicating arteries is not mentioned. Two cases were found in Schmidt's valuable paper on the material from the Commune Hospital, Copenhagen. The more recent case of Demay, Bertrand and Perisson [24] must be omitted for lack of accurate record. In this case a young woman aged 32 complained of failing vision, and later became maniacal. A large carotid aneurysm was found at post-mortem, reducing the chiasma and optic tracts to narrow bands. The authors frankly regret the omission of more detailed clinical notes on her vision.

Foster Moore has illustrated an admirable example of intracranial aneurysm of the ophthalmic artery, an extremely rare condition. This occurred in a man aged 35, who suffered from rheumatic endocarditis, and caused sudden blindness in the right eye. At post-mortem two months later the right optic nerve was found divided by an aneurysm of which he publishes an excellent coloured drawing [55]. Dempsey [23] and Schmidt [69] record other examples. Recently Sandford, Craig and Wagener have recorded a curious case with an altitudinal hemianopia due to aneurysmal dilatation of a cirsoid type in both ophthalmic arteries. Vision was greatly improved by cutting away the roofs of the optic canals to decompress the nerves.

The writer has omitted visual defects in arteriovenous (fistulous) cavernous aneurysms because the problem in that type is usually, but not always, different. There is never any difficulty in diagnosis, and such visual disturbances as occur are often of a kind beyond the scope of the present paper. For that reason Dandy's recent cases, Schmidt-Rimpler's and Dempsey's, amongst others, have been excluded. It may be added that an aneurysm of a saccular type often is present, even if it is fistulous, and it would be interesting sometime to evaluate the visual defects in such of these cases (and they are many) as are non-traumatic. The last condition is added because an optic nerve can be injured at the same moment that the skull is fractured.

COMMENTS ON THE SERIES.

Age-sex.—There is in my own cases a marked disproportion of the sexes, the majority being females (nine out twelve). In another series

(Group 3) of sixteen saccular aneurysms in the cavernous portion of the carotid all were females save one. In the series collected from the literature the discrepancy is not so great (F. 35, M. 31). Peculiar female vulnerability to cerebral aneurysm has been noted by Fearnsides and by Schmidt and seems to be a fact, in distinction to the acquired and often syphilitic aneurysms elsewhere in the arterial tree, which occur most often in males. As for age, most of those which have evolved in a neoplastic manner, relatively slowly, have occurred in patients over 30. But Foerster's case was 20, Schmidt's case 20, Packard's 21, Dempsey's 22, Conway's 23, and one of my own 23 (Case 11). The writings of Fearnsides, of Symonds and others, and our own experience, has familiarized us with the fact that congenital aneurysms may occur at all ages and that they are naturally common in youth. The pathology of the type of aneurysms under discussion seems in no way to differ from that of the so-called "berry" aneurysm, so well investigated by Eppinger [28], Wiley Forbus [33], by Drennan [26] and by Tuthill [84]. They mostly occur like other aneurysms, at the bifurcation of a large vessel, in this case the internal carotid, perhaps where the ophthalmic artery leaves it or, in the suprachiasmal group, at the point where the anterior cerebrals are joined by the anterior communicating.

SYMPTOMATOLOGY.

Some years ago it was a very generally accepted view that the diagnosis of an intracranial aneurysm presented a well-nigh insoluble problem. That this is no longer true is due to several developments, of which one of the most important has been the better understanding of tumour symptomatology, taking into account not only the situation of the lesion, but its pathology. It can be well understood that aneurysms must have been difficult to diagnose at a date when intracranial tumours were imperfectly understood, for the clinician could have had no safe starting point in his approach to the problem. At the present day we are better armed in our knowledge of the evolution of the tumour groups, and we have new weapons in X-rays and angiography which can often act in a decisive manner. On the whole the differentiation of aneurysms from other lesions which can interfere with vision centres around the pituitary adenomas and suprasellar tumours, and this immediately brings us to a consideration not only of the visual fields and X-ray appearances, but of certain other co-existent states, either of an endocrinal or neighbourhood type, which are common in one but not in the other. It must be borne in mind that the fields are to be linked with atrophic discs. A homonymous field defect with papilloedema is a neurological commonplace; the case is far otherwise when the nerve heads are atrophic. At the last analysis the differential diagnosis of a chiasmal lesion rests on the following points :—

(1) The nature of the field defect, coupled with the manner of its evolution (a point on which it is unusual to be able to gather detailed information) and the rapidity of its development.

(2) The degree of pain associated with the evolution of the visual defect.

(3) The co-existence of other neurological signs.

(4) The presence or absence of tuberal or endocrinal disturbance.

(5) The X-ray evidence.

Each one of these requires comment.

VISUAL FIELDS.

A study of the recorded cases brings to light one very important thing, the varying nature and pattern of the visual defects in the same patient at different times. For instance in Harris' case there was first blindness in both eyes with recovery; then a left central scotoma, then a right temporal hemianopia with a tendency to, but no certainty of, a right homonymous defect. Post-mortem findings made it certain that the homonymous defect was correct. Much the same fluctuations were present in Case 7 above, Foerster's case, and in Conway's. Conway's paper on his case indeed will repay careful study, for he includes diagrams of the visual fields taken on six occasions over a period of nine months showing wide variations in a bitemporal hemianopic defect, with remarkable spontaneous improvement continuing up to three days before his sudden death. Difficulties such as these impede the giving of a clear-cut analysis of the exact pattern of the visual loss in all the cases. With one eye blind and a temporal defect in the other it is always difficult to tell whether the field loss was basically bitemporal or homonymous, but the reader who runs his eye down the very abbreviated case histories in the synoptic tables will rapidly get an impression of the types that the cases have exhibited.

If the collected cases and the writer's own, 77 in all, are analysed the results are: (1) Bilateral amaurosis, 7 cases; (2) monocular central scotoma, amblyopia, or blindness, 25 cases; (3) the same, combined with temporal hemianopia in the contralateral eye, 10 cases; (4) homonymous hemianopia, 11 cases; (5) bitemporal hemianopia, 15 cases; (6) varia, examples in which analysis is difficult or not covered by the foregoing descriptions, 9 cases. The manner in which these variations of visual defect are brought about is worthy of inquiry. The section on complete blindness need not detain us very long (cases of temporary amaurosis from subhyaloid exudate are omitted). The writer's own case was curious and not without ambiguity, moreover the late history is unknown. In others the blindness was of sudden onset and chiasmal pressure authenticated by post-mortem dissection. The most important and largest combined groups are the second and third, monocular blindness with or without a temporal field defect in the other eye 33 cases.

It has already been stated that the commonest aneurysms to cause visual disturbance are those of the internal carotid. These may be supraclinoid or infraclinoid (cavernous) in position. It is strange that the latter which so often occur as a massive, saccular or fusiform non-fistulous type occupying the cavernous sinus should so rarely cause any defect of vision. The sac at necropsy may be in contact with the optic nerve, yet there has been no recognizable field defect. Recently McKinney, Achree, and Solz [54] have published four cases of this type with the usual associated paralysis of the nerves in the wall of the sinus (cavernous syndrome of Foix) and in these there has been a monocular upper nasal quadrantic loss. Packard and Zabriskie had a similar experience. Usually the lower and outer wall of the optic canal will be found to have been eroded in such cases. A more recent and admirable example is that of de Vet and Zeckel, which concerned a young man with total ophthalmoplegia, partial anæsthesia of the face, and blindness in the homolateral eye. In contrast with this group the aneurysm which springs from the supraclinoid part of the artery causes pressure on the optic apparatus which is certain, and usually immediate, in its effects. The pattern of the visual loss is by no means uniform.

Monocular amblyopia.—In the recorded cases the character of the monocular defect varies from dimness of vision, through various scotoma types, to blindness in the ipsilateral eye. It is probably very difficult for an aneurysm to remain so small that it compresses either the optic nerve, the chiasmal junction, or the tract alone, if it has sprung from the internal carotid artery. Sooner or later it is bound to compress two at least of these three components, and often all three. The post-mortem records often refer to pressure, not only on the optic nerve but on the tract and chiasma as well. The character of the field defect that results from an indentation of the outer edge of the chiasma is a very interesting subject for discussion and further study. Unfortunately very few fields have been examined by quantitative perimetry and there is very little information to be gleaned from the collected cases that would illustrate the unique compression which a carotid aneurysm can exert.

When the aneurysm has arisen from the internal carotid the field defects should be characteristic and allied to Traquair's "junction scotoma." The outer side of the angle of junction between the optic nerve and tract at the chiasma is one which no other lesion but an aneurysm can easily occupy. Now, the crossed fibres in the chiasma which form the knee, or loop, of Wildbrand and Saenger come sufficiently far across to be damaged by an indentation at that point, and thus arises the field picture which experience will probably show to be most characteristic of internal carotid supraclinoid aneurysms—a scotomatous or rapidly failing ipsilateral eye with a definitely homonymous hemianopic overlay in the fields of both eyes. If Wildbrand and Saenger are correct (they are confirmed by Balado) in their plan of the crossed fibres in the chiasma then the temporal defect in the opposite eye should be chiefly in the upper quadrant. The temporal field defect in the opposite eye may be more extensive than this by the time that the case comes first to skilled notice. For the aneurysm may extend chiefly backwards under the optic tract behind the chiasma, producing, of course, a congruous homonymous defect. But as a rule it will compress the junction of the ipsilateral optic nerve with the chiasma as well, so that it will be depressed acuity of the eye on the side of the aneurysm which excites comment and stimulates investigation. Some good examples will be found in Table III.

Central scotomata are by no means uncommon with pituitary adenomas, which arise medially, and should produce a well-equalized pressure effect in the prechiasmal space, but often do not do so. The capsule has a tendency to give way in an eccentric manner so that a nubbin of tumour breaks through under one optic nerve, stretching the nerve over it. In this way a central scotoma must develop. The basic field deficiency is, however, bitemporal, and the absence of pain, so rare a feature of the chromophobe adenomas, helps further to differentiate the cause.

Bitemporal hemianopia.—The production of a bitemporal field defect by a supraclinoid aneurysm is rarer (*see* Table V of collected cases). The defect may be produced by herniations of either the internal carotid the anterior cerebral, rarely the middle cerebral. When the aneurysm comes from the carotid it must break through the inner wall of the cavernous sinus, or arising at the origin of the ophthalmic artery pass medially under the optic nerve into the sella. Its enlargement there will produce a picture like that of an adenoma, with enlargement of the sella and possibly amenorrhœa (as in Case 12). But the fact that the aneurysm must always belong more properly to one side than the other leads to much greater loss of acuity on the one side. Thus it comes about that monocular scotomas may be associated not only with a homonymous defect, but also with a bitemporal. This happens frequently enough in pituitary adenomas and a differential diagnosis from the fields may not be possible. It is in these cases that the suddenness of onset of the malady, the pain accompanying it, and perhaps the occurrence of oculomotor palsies too, help in differentiation. The time factor becomes a most important one in differential diagnosis, and if it is not more stressed here it is because the case histories which have gone before emphasize the matter strongly enough. It may be noted that a sudden hæmorrhage into a pituitary tumour causes symptoms so like those of an intra- or parasellar aneurysm that differentiation may actually be impossible, unless acromegaly be present.

Bitemporal hemianopia produced by aneurysm of the anterior cerebral may eventually have nothing in its form to denote its cause, but in the early stages the loss is in the inferior temporal fields, rather than the superior as in pituitary adenomas. Such a finding is characteristeric (*see* Cases 7 and 9) and can scarcely be mimicked by indentation of the dorsum of the chiasma by normal, but stretched, anterior cerebrals with a massive pituitary tumour below. Later, when the bitemporal hemianopia is fully developed we must depend on the ancillary diagnostic points already outlined.

Homonymous hemianopia.—A few cases of homonymous hemianopia are to be found in Table III, those which have already been discussed as complicated by an additional defect in the eye on the side of the aneurysm, others are given in Table IV. Curiously enough the defect was only once produced by an aneurysm of the posterior cerebral artery. Usually it arose from the carotid or from the middle cerebral or even from the anterior cerebral; the last seems strange. Reference to fig. 1 will show, however, that it is quite possible for an aneurysm arising in any part of the Circle of Willis to reach and compress tractus opticus quite easily, insinuating itself backwards and outwards either above or below the chiasma.

It can be concluded that the most characteristic fields of aneurysms (the fundi being normal or atrophic) are therefore: (*a*) A scotomatous homolateral eye, with an overlying homonymous defect in the nasal field of that eye and in the temporal field of the other; (*b*) bitemporal defects, only clearly aneurysmal because of inferior quadrantic loss as the earliest sign, or because of the suddenness of development, or because of ocular muscle palsies, as well as pain; (*c*) nasal hemianopia in the ipsilateral eye.

OTHER NEUROLOGICAL SYMPTOMS AND SIGNS.

Pain and headache.—Pain is a far more frequent accompaniment of aneurysms than of pituitary adenomas. It is not rare for the latter to progress to severe chiasmal compression and blindness without the patient suffering any noteworthy pain at all. This is certainly true of the chromophobe adenomas. The alpha-granule type of acromegaly is often an exception to this rule, but it is by no means sure, even in these cases, that the pain is due to sellar expansion. In many cases the pain seems to be due to tensile changes in the bone, for whilst the acromegalic patient may, and often does, complain of severe headache, he has much the same pain in his back and limbs. On the other hand, the aneurysmal subject has pain of very great severity, often agonizing in degree, and of abrupt onset. In many cases the pain is local in the forehead, or at least it is unilateral. This pain may be accompanied by local numbness in the forehead (in Cases 4 and 5 it was general over one trigeminal field) and if this is abrupt in its origin diagnosis is immediate and certain. The characteristic anæsthesia of the ophthalmic division of the 5th nerve, so striking a feature of the subclinoid aneurysm, which does not usually compress the chiasma or optic nerve, does not occur in supraclinoid aneurysms which affect vision more frequently. Severe pain in some form or another, appearing suddenly, and roughly contemporaneously with a disturbance of vision, must always strongly suggest aneurysm.

Hemiparesis.—Weakness of the limbs of a transitory kind, numbness or tingling in the hands or feet, are rare accompaniments of aneurysm. Hemiparesis occurred in two of the cases in this series and will be found to have been present, occasionally only, amongst the collected cases.

Mental changes.—The high incidence of aneurysms, especially of massive type, at necropsies in asylums must have a meaning. This is surely not that the insane are particularly liable to develop aneurysms, but that aneurysms can often lead to insanity. In the writer's own series there have been two cases in which at the time when first seen mental deterioration was the outstanding feature. One was Case 5, the other, a woman aged 50, not included in this series, with unmistakable signs of infraclinoid carotid aneurysm of eight months duration, and mental disturbance developing almost immediately after the ocular palsies and pain which heralded the formation of the aneurysm. Some form of mental derangement was not uncommonly present in the cases collected from the literature, notably in the examples of Byrom Bramwell, and of course, Beadles. It seems likely that it is circulatory failure, rather than the pressure of aneurysmal mass, which causes these alterations in behaviour and character which are apt to make the patient a fit subject for segregation in an asylum.

Oculomotor palsies.—Ophthalmoplegia, either total or incomplete, is the characteristic picture produced by aneurysms of that part of the carotid artery which lies in the cavernous sinus (i.e., in its sub-clinoid portion). As has been said, it is only rarely that this particular aneurysm produces any defect of vision. In Cases 4 and 5 in the present series ptosis from 3rd nerve palsy was present, and diplopia was an early feature in Case 12. It may be said that any case in which severe pain in the head is followed by diplopia there will always be a strong suspicion that an aneurysm had produced it. This would be more likely still if the pain was specially referred unilaterally to the forehead and the diagnosis would be certain if hypoæsthesia or numbness rapidly developed. Of course diplopia after headache is a common feature of raised intracranial pressure. It is the quality of the pain, and the rapidity of appearances of the ocular palsy, which distinguishes the aneurysmal cases. Abducens palsy in association with evidence of chiasmal compression is commoner with aneurysm than with pituitary adenomas, for the nerve is insulated from the sella by the carotid artery, on the outer surface of which vessel it lies. A good example was Case 10. The writer has seen three cases of pituitary adenoma with oculomotor paralysis, and it is indeed curious that a frank lesion of the motor nerves to the eyeball is not a commoner feature of pituitary tumours. In actual fact diplopia is not infrequent with them, but the buffering of the nerves by the carotid artery saves them from direct and obvious paralysis.

Anosmia.—This ought to be a common symptom in aneurysm, but it is almost always absent, though uncinate attacks are not uncommon (Case 8), as would be probable with a tumour so close to the uncus. Anosmia is only produced by lesions which compress the olfactory bulbs, the nerve itself stands displacement and light compression very well.

Tuberal signs.—Somnolence, sweating, visceral disturbance, temperature variations, cardiac rate and rhythm variations are all too recent tuberal or hypothalamic signs to have produced instructive comments in the literature of aneurysms. In the series recorded above nothing was noted but change of water balance in two cases, but in neither was it striking. Polyuria and polydipsia is mentioned by Van Bogaert *et al.*, and by Lodge *et al.* No doubt much more information on these points will come in future. But it is unlikely that hypothalamic signs will occur in any great degree because it requires an invasive, destructive lesion of tuberal centres or pathways to induce them. In a fairly large experience of third ventricle lesions the writer has been impressed by the absence of autonomic signs if the tumour or cyst merely indents or presses on the neighbourhood structures without cutting into them.

Dyspituitarism.—The basal metabolic rates are given above in some of my own cases. In only one (Case 11) was there any notable change, a decrease suggestive of hypopituitarism. This patient and another male (Case 9) had the slightly yellowish skin suggestive of a pituitary adenoma. The question of amenorrhœa next arises, and in only one case (Case 12) did it introduce serious doubt in the interpretation of the cause of the visual defects and in general as to her malady. Unless the aneurysm fills the sella turcica and severely compresses the pituitary, as it did in Cases 5, 7, 10 and 12 of the females, no change in menstrual periodicity is likely. It so happens that only in Case 12 was the patient of such an age that the history of an eight year amenorrhœa could be held to be significant. This, then, is at first sight an important differential point, but given a pituitary adenoma in a female at or beyond menopausal age and it is clear that reliance must be placed on other things, such as the occurrence of severe, or even agonizing, pain at the beginning of the visual troubles and that no important conclusion can be arrived at from a consideration of endocrinal disturbances alone.

The X-ray appearances.—These must be grouped under two headings: (*a*) Opacity in the wall of the aneurysm; (*b*) alterations in the bones of the base of the skull.

(*a*) *Opacities in the wall of the aneurysm.*—The loss of the muscular coat and elastic fibres, the characteristic change in the aneurysmal walls with the conversion of the vessel into a fibrous sac, is accompanied frequently by the deposit of calcium salts. Such patches of calcification could be seen in the radiographs of Cases 5, 9 and 10. Although many aneurysms, when they have reached this stage, stabilize and grow slowly, they are none the less capable of further expansion at some point. I have, on the other hand, followed a case for fourteen years and seen little change in the aneurysm on periodical X-ray examinations. In Case 9 above there has been an increase in symptoms, although there is a shell of well-calcified wall in the greater part of its extent. The calcification can, by the nature of the communication of the sac with the great vessel, never be complete, and there will be weak places at the neck of the sac. It is well known, similarly, that however well an aneurysm may be filled with clot, it yet may rupture at that part where it is still filled with circulating blood, as happened in Case 8. The fine line of calcification seen in X-ray pictures is unlike that of any other intracranial lesion. When seen as more or less complete circles, they have been called, for no very good reason, "Albl's rings." It is the density and narrowness of the line which is diagnostic. Occasionally small plaques of calcification can be seen in the walls of the vessel within the larger circle, and difficulties can then arise as to whether we are faced with a cyst of the pituitary anlage or teratoma. In the latter the calcification is generally more irregular, and rarely so high in the cranium. There are cases, however, in which there will be difficulty in interpretation, others will be simple. The calcification seen in gliomas, epidermoids, and in dural exotheliomas can never cause any difficulty in differentiation.

(*b*) *Alterations in the skull.*—Destruction of the sella turcica is the most frequent and most obvious effect of carotid aneurysms. The sellar patterns in the present series of cases confirms the fact that though the alteration can closely simulate that of the pituitary adenoma, more often it is not likely to cause confusion. The tendency is towards lateral erosion of the sella and damage to the anterior clinoids, especially that of the same side, a point not always easily established unless special care is taken to demonstrate the clinoid processes. Aneurysms of the anterior end of the carotid have a particular tendency to widen the sphenoidal fissure, a feature illustrated by three of these cases. This enlargement can be seen in the ordinary anteroposterior views, but it is particularly well demonstrated by oblique views of the orbit showing up the optic canals. The writer has referred to this elsewhere [47]. In this tangential view another feature is visible, erosion of the lower and outer wall of the optic canal, a point which Twining and the writer have come to regard as almost, if not quite, pathognomonic. The internal carotid curves forwards to the back of the sphenoidal fissure, and upwards to the inner side of the anterior clinoid process. A blow-out in this situation will damage both in course of time, it will porose the strut of bone which passes from the side of the body of the sphenoid to the lesser wing to complete the optic foramen below. The only other lesion likely to damage this bridge of bone would be a dural exothelioma arising from the back of the wing of the sphenoid and floor of the temporal fossa anteriorly. There is one such case amongst my recent material, but there was loss of all the structure in the sphenoidal wing, a general blurring, not likely to be mistaken for an aneurysm, whilst the optic foramen had in that case disappeared altogether.

It would be impossible to stress too heavily the help which these auxiliary aids to diagnosis can give. There is no other way of knowing what is the state of the sphenoid and optic canal, information which must be correlated with the clinical history and findings for the making of a correct diagnosis, except by taking special oblique X-ray views.

Angiography.—In no cases can Moniz's method of angiography be of greater service. Angiography has become a well-accepted diagnostic aid and when the results are positive the solution of what may have been a clinical puzzle is certain. It is important to recognize that it may fail, either through faults in technique or through an aneurysm having too small a cavity to throw a clearly distinguishable shadow amongst a maze of branches. The best pictures are given by saccular aneurysms in direct communication with the internal carotid itself and are less certain if it springs from a subsidiary vessel. The advantage of angiography is obvious, for it does away with the need for what might be a hazardous exploration and tells us more definitely than any other method from precisely which artery the aneurysm has arisen, thus giving a definite lead to vessel ligature, if that should be thought desirable. The actual size of the scour or tuft of thorotrast seen in the aneurysm may be disappointingly small, but it will usually be of sufficient size to be unmistakable. The writer has not used angiography in all his cases because he is not yet entirely convinced that it is a completely harmless procedure.

TREATMENT.

I feel more and more convinced that there is only one useful treatment for these cases, and that is carotid ligature. The cases recorded in this paper do not show much evidence of this belief, for the carotid was tied only in Case 11. However they must be regarded as an attempt to clarify the clinical picture of aneurysm, an exercise through which treatment has emerged. Without going into the operative question in great detail, one or two broad principles can be laid down. Ligature has been the treatment for aneurysm since the days of John

Hunter. The treatment might therefore be applied to these particular aneurysms without equivocation, without reservation, if it were certain that tying the carotid would do no harm. Allowing for the fact that the dangers of carotid ligature have been exaggerated, there is no doubt that there are risks, nor is there any absolutely sure way in which they can be avoided. This being so, only those cases will be operated upon where progressive failure of vision, or where persistent and wearying pain, make intervention imperative. And even in these, the carotid will only be tied if it can be proved that digital compression for half an hour is tolerated without ill-effect. Furthermore, when the operation is undertaken, the final ligature will not be applied until the effects of a temporary one have been observed for a full hour (local anæsthesia is a *sine qua non*). By such means as these the majority of disasters ought to be avoidable. I have tied the internal carotid nine times and the common carotid twice. In one case only was there any anxiety, on account of a temporary aphasia, which cleared up later. Clearly carotid ligature is of no use for aneurysms far removed from the main trunk. Some of the more accessible ones may come very occasionally to be excised. Tönnis has already removed a small aneurysm of the anterior cerebral artery. Dott has packed muscle round one, whilst the writer has also packed one with muscle and partly cut it away (an anterior cerebral aneurysm burrowing into the right frontal lobe and not affecting vision). In the end each case will be treated on its own particular merit.

SUMMARY.

(1) Twelve cases of intracranial aneurysms affecting the visual pathways are reported out of a personal series of fifty-three aneurysms.

(2) Sixty-six previously recorded cases are analysed.

(3) The present series is compared with the writer's other aneurysmal material.

(4) The twelve cases are divided into four groups according as they interfere with the visual cortex, those that compress the optic tract, the chiasma, and the optic nerves.

(5) The field defects in these lesions are fully discussed and certain characteristics emphasized either in pattern or manner of development.

ANALYSIS OF RECORDED CASES.

I.—BLINDNESS (7 CASES).

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Stilling 1883	F.	42	Sudden blindness; later P.L. in L. eye. Mydriasis	Fell unconscious; recovered in an hour. Died in 24 hours	R. int. carotid, size of walnut, compressing chiasma and tuber
Ogle 1865	M.	—	Blind 4 years	Paraplegic 12 years. Imbecile lately	Small aneurysm L. anterior cerebral, compressing L. optic tract
Hanot 1872	F.	50	Blind L. eye 8 years. Blind R. eye 2 years.	Deafness 10 years. Fits 8 years. Intelligence impaired. 18 months; later deaf, blind and imbecile	Aneurysm 5 × 3 cm. L. cerebral, compressing chiasma and both optic nerves. It was embedded in the 3rd ventricle
Hutchinson, J., jun. 1889	M.	20	Sudden loss of sight. Hæmorrhage into retina	Paresis R. arm and leg	Aneurysm of basilar artery compressing chiasma from behind
Wildbrand and Saenger 1915	M.	55	Sudden blindness. Fundi normal	W.R. +. Survived 6 days	Chiasma flattened and compressed by aneurysm of L. internal carotid
Van Bogaert, Helsmoortel and Nyssen 1929	M.	37	Sudden blindness L. eye 8 days; later R. eye. Bilateral papillœdema	Polydipsia. Polyuria. Severe head injury 3 years before	L. anterior cerebral compressing chiasma from above
Jefferson 1937 Case 6	F.	60	Fundi not visible. Blind both eyes	None	Recovery. Unverified

II.—Monocular Amblyopia, Central Scotoma, or Blindness (25 Cases).

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Nebel 1834	F.	28	Blind R. eye	—	Aneurysm right anterior cerebral compressing L. optic nerve
Hare 1850	F.	18	Dimness of vision L. eye	L. ptosis, 3 weeks	Died suddenly. L. posterior communicating artery compressing L. optic nerve and tract
Roe 1850	F.	21	R. eye blind 3 mths.	Violent headache 15 mths., then drowsy. Weakness L. face	Anterior cerebral aneurysm size of hen's egg, right half of sella, optic nerve and chiasma flattened. R. olfactory nerve compressed
Giraudet 1857	F.	52	Blind R. eye 2 years	Headache 2 years. Anosmia. Intelligence impaired	Aneurysm 4 × 2·5 cm. at R. side of sella, optic nerve flattened, ribbon-like
Blessig 1877	M.		L. eye blind. High-grade choke	Exophthalmos. L. 3rd nerve palsy	Internal carotid. Died 35 days after ligature
Czermak 1902	F.	59	Blind L. eye, recent	Abducens palsy, 6 years, neuralgia brow and face, 4 years. Ptosis L. recently	Aneurysm L. internal carotid found at autopsy
Beadles (Nettleship) 1907	F.	61	L. amblyopia, 18 yrs. L. optic atrophy	L. ophthalmoplegia	L internal carotid in cavernous sinus pressing on L. optic nerve
Reinhardt 1913	M.	41	Blind L. eye	L. oculomotor palsy, complete	Not verified. X-ray destruction of sella. Recovery
Fearnsides 1916	F.	41	Blind R. eye	Anæsthesia ophthalmic division of trigeminus	Aneurysm size of small grape R. anterior cerebral
Shannon 1917	F.	52	R. central scotoma, R. optic atrophy	Paresis L. side	R. internal carotid compressing R. optic nerve
Groedel 1921	M.	41	L. optic atrophy 8 yrs. L. eye blind	L. ophthalmoplegia, slight exophthalmos	X-ray dilatation of sella. Transphenoidal operation and death from hæmorrhage. L. internal carotid, size child's fist
Cushing 1923	F.	52	Progressive amblyopia, central scotoma R.	Died suddenly some months later	R. internal carotid compressing chiasma
Cutler 1923	F.	45	Progressive failure vision R. eye. Pallor of disc. Enlarged blind spot	Nil	Died. "Circle of Willis"
Kirby 1924	M.	60	Diminished acuity, irregular contraction visual fields, pallor R. optic nerve, L. normal	Complete R. ophthalmoplegia for 34 yrs. Anæsthesia R. trigeminus. Injury 34 years ago. X-ray, mass in R. middle fossa	Necropsy. Aneurysm R. internal carotid

II.—MONOCULAR AMBLYOPIA, CENTRAL SCOTOMA, OR BLINDNESS—*Continued.*

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Packard and Zabriskie 1925	M.	21	Nasal hemianopia in R. eye only. Bilateral papillœdema	L.-sided convulsions. L. pyramidal signs	R. middle cerebral compressing R. optic nerve
Birley and Trotter 1928	M.	28	Amblyopia. Pallor R. disc	Followed severe head injury. Paresis R. 3rd, 4th and L. 6th and 7th. Violent epistaxis. Bruit present	Recovery after ligature of R. internal and external carotids
Brunetti 1931	F.	63	Failing vision, R. eye	R. ptosis	X-ray diagnosis. Calcification in region of R. internal carotid and ophthalmic arteries
Schmidt 1931	F.	58	R. amblyopia 16 years, blind 9 years	Ophthalmoplegia R., 11 years. R. trigeminal neuralgia	Aneurysm size of hen's egg, R. middle fossa compressing optic nerve
Garvey 1934	F.	55	Atrophy R. optic nerve, bilateral chorio-retinitis	Ptosis R. 2½ years. Weakness of legs. W.R. +	Aneurysm 3 cm. diameter in interpeduncular space, R. internal carotid, compressing R optic tract, R. crus, and pons
McKinney, (1) Acree, and Soltz 1936	M.	56	Slight pallor L. disc. R. normal. Constriction of L. visual field especially temporal	L. ptosis and ophthalmoplegia	X-ray diagnosis: calcification in aneurysm
(2)	F.	42	Pallor temporal part, L. disc. R. normal. Constriction visual field on nasal side L	Complete ophthalmoplegia L Hypæsthesia V.1 and V.2. Bruit over eyeball	X-ray diagnosis: calcification in wall of aneurysm
(3)	M.	57	Marked pallor, L. disc. R. normal. Blind L. eye 2 yrs. R. normal	Ophthalmoplegia partial. L. hypæsthesia V.1	Unverified. Suggestive X-ray findings
(4)	F.	54	R. papillœdema. L. normal. Blind R. eye	Ophthalmoplegia R. Hypæsthesia V.1, 2 and 3	X-ray diagnosis: calcification in wall of aneurysm
De Vet and Zeckel 1937	M.	19	Became blind in L. eye, sight depressed on R. side	Complete ophthalmoplegia and anæsthesia of ophthalmic division of trigeminal, L. Wassermann + 1 in 10	Transfrontal exploration; angiographic verification. Ligature of internal carotid artery. Recovery
Jefferson—Case 5	F.	50	Pallor L. disc. Vision, R. $\frac{6}{6}$, L. $\frac{6}{60}$	L. ophthalmoplegia, incomplete. L. trigeminal anæsthesia R. hemiparesis X-ray enlargement of superior orbital fissure. Shadow of large aneurysm in L. middle fossa	Necropsy: aneurysm size tangerine orange, L. internal carotid occupying L. middle fossa

It is difficult to see how a visual defect can be purely monocular unless the aneurysm compresses the optic nerve right up against the optic foramen, and compressed nothing else. It is certain that many cases in the Table above must have had more complex disturbances of vision than were discovered. The first three cases demonstrate this quite clearly, but both Hare's and Roe's cases must have had visual field defects in the eye which is not mentioned. A bibliographer can, however, only transcribe cases as they are recorded, however sure he may be that under modern conditions other signs would have been evoked.

III.—MONOCULAR AMBLYOPIA WITH TEMPORAL HEMIANOPIA IN CONTRALATERAL EYE (10 CASES).

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Bramwell 1906	M.	38	Blind R. eye, temporal hemianopia on L.	Mental changes. Died 5 years later	L. internal carotid, very large
Cushing 1912	M.	31	L. homonymous hemianopia, later, blind in L. eye	None. Died suddenly 3½ years later	R. internal carotid; also a pituitary adenoma
Symonds 1924	M.	25	L. homonymous hemianopia. R. amblyopia	Infective endocarditis. Partial 3rd nerve palsy. L. hemiparesis and hemianæsthesia	Aneurysm size of hazel nut between R. optic nerve and temporal lobe
Harris 1928	F.	46	Sudden blindness, then recovery. Optic pallor, central scotoma L., temporal hemianopia R., tendency to R. homonymous defect earlier	Sudden diplopia, 7 years earlier. Recovery. None when observed	L. anterior cerebral compressing chiasma and L. optic tract
Albl 1929	M.	59	Blind L. eye, optic atrophy. R. temporal defect	X-ray, sellar distortion. Fine shell of calcification in wall of aneurysm	L. internal carotid, adherent to chiasma
Dott 1933	F.	36	L. eye blind. R. temporal defect	None	L. internal carotid
Elsberg and Dyke 1934	F.	57	1933—Amblyopia L. eye. 1934—L. eye blind. R. temporal hemianopia	None	Operative verification; aneurysm 2 × 2 cm., origin not discerned. Recovery
McKendree (1) and Doshay 1936	F.	46	Pallor R. disc, L. normal. Almost blind R. eye, temporal field defect L.	Nil. X-ray negative	Operative disclosure of intrasellar aneurysm
(2)	F.	31	Blind L. eye, fundi normal. Temporal defect R. field	Amenorrhœa 10 yrs. Sella porosed, not enlarged	Operative disclosure of intrasellar aneurysm
Jefferson—Case 8	F.	49	Atrophy R. disc, blind. Pallor, L. temporal hemianopia	Sella normal. Shell of suprasellar calcification on X-ray	Thorotrast verification

In the above group the temporal defect was, no doubt, sometimes due to a tract compression and was basically part of a homonymous hemianopia. In other cases it was due to compression of the chiasma and would be part of a bitemporal visual loss. My own Case 8 was of the latter kind.

IV.—HOMONYMOUS HEMIANOPIA (11 CASES).

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Henneberg 1906	F.	40	L. homonymous hemianopia. Flickering lights before L. eye	Headache. Pain, R. trigeminal area, 14 days, then several epileptic fits. Died in stupor	Aneurysm L. anterior cerebral 1 cm. long in olfactory trigone, compressing L. optic nerve.
Gehrung 1914			Homonymous hemianopia	——	Internal carotid.
Freund 1916	F.	70	R. hemianopia, 8 years. Normal eye-grounds.	Tabes dorsalis. W.R. +	L. internal carotid, spindle-shaped aneurysm pressing on L. optic tract.
Foerster 1921	M.	29	Sudden blindness both eyes, vision returned. Later hemianopia	L. hemiplegia	Middle cerebral.
Aliquo-Mazzei 1929	M.	61	R. homonymous hemianopia. Pallor of both discs	Complete R. Ophthalmoplegia	R. internal carotid.
Dott 1933	M.	58	R. upper quadrant incongruous homonymous hemianopia	None	R. anterior cerebral.
Sjoqvist, O. 1936	M.	72	Retinitis. No optic atrophy. L. homonymous hemianopia.	Anosmia. Psychological changes. Arteriosclerosis	Large R. carotid aneurysm demonstrated by thorotrast.
Jefferson— Case 1	M.	47	L. homonymous hemianopia. Fundi normal.	History of subarachnoid hæmorrhage. Slight L. hemiparesis. Later fits	Unverified pathologically. Recovery.
Case 2	M.	38	R. homonymous hemianopia. Fundi normal	History of subarachnoid hæmorrhage. Dysphasia. Later fits	Recovery. Unverified pathologically.
Case 3	F.	54	Fundi normal. Acuity normal. R. homonymous hemianopia	Visual epilepsy in R. visual field	Recovery. Unverified.
Case 4	F.	29	Amaurosis, recovery; then L. homonymous hemianopia. Fundi normal	History of subarachnoid hæmorrhage. R. 3rd nerve palsy. R. trigeminal hypæsthesia. L. hemiparesis	Necropsy: aneurysm R. posterior cerebral compressing optic tract and crus.

V.—BITEMPORAL HEMIANOPIA (15 CASES).

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Weir Mitchell 1889	M.	48	Bitemporal hemianopia 2 yrs. Pallor of discs	Attacks of weakness in arms and legs, occasional dragging R. foot. Sudden coma and death	Aneurysm dorsal to chiasma (? abnormal anterior arteria communicans), separating optic nerves
Noissewski 1901	M.	31	Bitemporal hemianopia, choked discs	None	L. carotid artery tied. Recovery
Bramwell 1906	M.	31	Bitemporal hemianopia, later completely blind	Dementia later. Injury 15 years before	R. internal carotid, size of orange, stretching optic nerves
Kümmell 1911	M.	37	Bitemporal hemianopia, then R. eye blind. L. vision in lower visual quadrant only	None	R. internal carotid (? R. anterior cerebral)
Posey 1911	F.	62	Bitemporal hemianopia, bilateral optic atrophy	None	L. internal carotid pressing on chiasma
Conway 1926	M.	23	Bitemporal hemianopia, then blindness in both eyes, later return of vision	None. Died suddenly after 9 mths.	R. middle cerebral
Foggie 1927	F.	56	Bitemporal hemianopia. Trace of papillœdema R. L. normal	R. ophthalmoplegia 4 months. Headache, vomiting, 5 weeks. Severe pain and anæsthesia R. forehead	Recovery. Condition not much changed one year later
Pfingst and Spurling 1929	F.	54	Bitemporal hemianopia	Sudden recurrent 3rd nerve palsies	X-ray : calcified area lying to R. of sella. Recovery
Trevani 1934	M.	34	Progressive bitemporal hemianopia 8 years; blind L. eye 1 year. Primary optic atrophy	None	Operation. Aneurysm 5 × 4 × 3 cm. internal carotid L.
Sjoqvist, O. 1936	M.	58	1924 temporal hemianopia R. eye. Later blind both eyes	Hypopituitarism. Sellar destruction 1934	Died after operation. Huge aneurysm filling sella turcica
Wakeley 1937	M.	44	Bilateral optic atrophy. Bitemporal hemianopia. 10 years' history	Epileptic fits recently. X-ray, suprasellar calcification	Operative and post-mortem verification. Aneurysm of anterior communicating artery
Jefferson— Case 7	F.	36	Pallor R. disc, acuity $\frac{6}{9}$. L. normal, $\frac{6}{12}$. Bitemporal hemianopia	None. Sella normal	Operative verification. Aneurysm of R. anterior cerebral artery
Case 10	F.	56	V.A.R. $\frac{6}{9}$, V.A.L. C.F. L. disc pale. L. central scotoma, bitemporal defects	None except enlargement of sella	Operative verification, aneurysm L. internal carotid (infra-clinoid)
Case 11	M.	23	Pallor of both discs. V.A.R. $\frac{6}{18}$, L. $\frac{1}{60}$. Bitemporal hemianopia	Enlarged sella, erosion L. optic canal	Operative verification. L. internal carotid ligatured. Recovery
Case 12	F.	46	R. optic atrophy, acuity $\frac{6}{36}$. L. disc normal, acuity $\frac{6}{6}$	R. abducens paresis. L. paresis superior rectus. X-ray: enlarged sella. Amenorrhœa 8 years	Operative verification. R. internal carotid

VI.—VARIA (9 CASES).

Author	Sex	Age	Visual defect	Other clinical findings	Site of aneurysm
Rice 1904	F.	65	Failing vision for 10 years	Epilepsy	R. anterior cerebral size 3·4 × 2·9 cm. pressing on chiasma and R. optic nerve
Kennedy 1916	F.	53	Blind R. eye, pallor of disc. Central scotoma, L. eye	Slight weakness L. arm, depressed abdominals, L.	Died. R. internal carotid
Taylor 1923	F.	46	V.A.R. and L. $\frac{6}{60}$. Six months later L. eye blind, limited central vision on R.	Nervous breakdown and diplopia some years before	Died. Large sac from anterior cerebral artery compressing both optic nerves
Denray *et al.* 1926	F.	32	Failing vision	"Meningismus" 3 years earlier. Second attack followed by insanity	R. internal carotid, compressing the chiasma
Lodge, Walker and Stewart 1927	F.	52	Amblyopia L. eye, 9 months. R. 2 months. Later, blind L. eye, nasal field defect R. eye	Polyuria. Finally sudden flashes of light before eyes. Vomiting, coma. Died suddenly	L. internal carotid; 3·5 cm. diameter, deeply projecting into interpeduncular space. Optic tracts and chiasma stretched ribbon-like over the mass
Schmidt 1931	F.	40	Amblyopia R. eye, later blind Later, failing vision L. eye	None	Spherical aneurysm, size of plum. R. internal carotid compression chiasma
Cutler and Zabriskie 1933	M.	25	Blind R. eye. Primary atrophy. Failing vision L.	Palsy R. 6th and partial of 3rd nerve. Anæsthesia R. $V^1 + V^2$. (Injury 3 years before) Large sella	Huge aneurysm R. internal carotid, chiasma elevated and pushed to L. Aneurysm filled anterior part of R. middle fossa. Post-mortem
Sjoqvist, O. 1936	M.	48	Inferior quadrantic binasal hemianopia. Later L. eye blind from retinal thrombosis	Blood-pressure 300 Hg. Anosmia	Presumptive diagnosis after thorotrast injection. L. internal carotid aneurysm
Jefferson— Case 9	M.	59	Bilateral optic atrophy. V.A.R. $\frac{1}{60}$. V.A.L. $\frac{6}{24}$. Altitudinal hemianopia	X-ray: calcification of sellar aneurysm	Thorotrast verification. L. internal carotid

REFERENCES

[1] ALBL, H. "Aneurysma der Carotis interna einen Hypophysen Tumor vortauschend; ein Beitrag zur Diagnose intrakranieller Aneurysmen," *Fortschr. a. d. Geb. d. Roentgenstrahl.*, May, 1929, 39, 390.

[2] ALBRIGHT, F. "The Syndrome produced by Aneurysms at or near the Junction of the Internal Carotid and the Circle of Willis," *Bull. Johns Hopkins Hosp.*, 1929, 44, 215.

[3] ALIQUO-MAZZEI, A. "Contributo alla conoscenza della sindromi oculari da aneurisma della carotide interna," *Boll. d'Oculo*, 1929, 8, 1187.

[4] Balado, M. "Das Corpus Geniculatum Externum," Berlin, 1937.

[5] Beadles, C. F. "Aneurisms of the Larger Cerebral Arteries," *Brain*, 1907, **30**, 285.

[6] Blane, G. "History of Some Cases of Diseases of the Brain, &c." Trans. of a Society for the Improvement of Med. and Chir. Knowledge. London, 1800, **2**, 192.

[7] Birley, S. L., and Trotter, W. "Traumatic Aneurysm of the Intracranial Portion of the Internal Carotid Artery," *Brain*, 1928, **51**, 184.

[8] Blessig. "Aneurysm of Left Internal Carotid," *St. Petersburg Med. Journ.*, 1877.

[9] Borchardt, M. "Die chirurgische Bedeutung der Gehirnaneurysmen," *Beit. z. Klin. Chir.*, 1925, **133**, 429.

[10] Bramwell, Byrom. "Intracranial Aneurysms" in "Clinical Studies," Edinburgh, 1906, 288.

[11] Bramwell, Edwin. "A note upon the Ætiology of Recurrent and Periodic Ocular Palsy and Ophthalmoplegic Migraine," *Trans. Ophthal. Soc.*, 1934, **54**, 205.

[12] Bristowe, S. S. "Aneurysm of the Intracranial Portion of the Left Internal Carotid Artery," *Trans. Path. Soc. Lond.*, 1868, **19**, 174.

[13] Brunetti, L. "Studio Rontgenologico della calcificazioni della carotide interna e dell'arteria oftalmica," *Riv. di Rad. e. Fis. Med.*, 1931, **3**, 567.

[14] Chevalier, T. W. "Aneurysmal Tumour Situated Between the Brain and Sella Turcica," *Lond. Med and Phys. Journ.*, 1827. New Series 3, pp. 498/501.

[15] Coe, R. W. "Case of Aneurysm of the Left Internal Carotid within the Cranium," *Assoc. Med. Journ. Lond.*, 1855, **3**, 1069.

[16] Conway, J. A. "Two Cases of Cerebral Aneurysms Causing Ocular Symptoms with Notes of Other Cases," *Brit. Journ. Ophth.*, 1926, **10**, 78.

[17] Copland, S. *Monthly Journ. and Rev.*, 1825, **3**, 443.

[18] Cushing, H. "Contributions to the Study of Intracranial Aneurysms," *Guy's Hosp. Reports*, 1923, **73**, 159.

[19] *Idem.* "The Pituitary Body." Philadelphia, 1912.

[20] Cutler, C. W. "Disease of the Optic Nerve and its Relation to the Posterior Nasal Sinuses," *Arch. Ophthal.*, 1923, **52**, 331.

[21] Czermak. Verein deutscher Aerzte in Prag., *Prag. Med. Wochenschr.*, 1902, **27**, 227.

[22] Delpech, M. "Tumeur anévrysmale de la base du cerveau," *Bull. de la Soc. Anat.*, Paris, 1845, **17**, 112.

[23] Dempsey, A. "Case of Orbital Aneurysms," *Brit. Med. Journ.*, 1886, **2**, 541.

[24] Demay, M., Bertrand, I., and Perisson, J. "Anévrysme de la carotide interne ayant simulé une tumeur cerebrale," *Rev. Neurol.*, 1926, **33**, 1027.

[25] Dott, N. "Intracranial Aneurysms," *Edin. Med. Journ.*, December, 1933, p. 219.

[26] Drennan, A. M. "Aneurysms of the Larger Cerebral Vessels," *New Zealand Med. Journ.*, 1921.

[27] Elsberg, C. A., and Dyke, C. G. "Meningiomas Attached to the Mesial Part of the Sphenoidal Ridge," *Arch. Ophth.*, 1934, **12**, 644.

[28] Eppinger, H. "Pathogenesis der Aneurysmen," *Arch. f. klin. Chir.*, 1887, **35**, 1. (Supplement.)

[29] Fearnsides, E. G. "Intracranial Aneurysms," *Brain*, 1916, **39**, 225.

[30] Foerster, O. "Aneurysma der carotis interna," *Berl. klin. Wochnschr.*, 1921, **58**, 1057.

[31] Foggie, W. E. "Aneurysms of the Internal Carotid in the Cavernous Sinus" *Edin. Med. Journ.*, 1927, 649.

[32] Foix, C. "Syndrome de la Paroi externe du Sinus Caverneux," *Rev. Neurol.*. 1922, **38**, 827.

[33] Forbus, Wiley. "On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries," *Johns Hopkins Hosp. Reports*, 1930, **47**, 239.

[34] Freund, C. S. "Subdural gelegenes Aneurysm der Carotis interna als Ursache der Kompression eines Tractus optici (homonyme Hemianopsie)," *Klin. Monatsbl. f. Augenheilk.*, 1916, **56**, 468.

[35] Garvey, P. "Aneurysm of the Circle of Willis," *Arch. Ophthal.*, 1934, **11**, 1032.

[36] Gehrung. *New York Eye and Ear Hospital Reports*, 1914.

[37] Giraudet, E. "Observations sur les anévrismes intracraniens," *Gaz. des Hôp.*, 1857, p. 105.

[38] Groedel, G. R. "Roentgendiagnostik in der inneren medizen und der Grenzgebieten," Bd. VII. Munich, 1921.

[39] Gull, W. "Cases of Aneurism of the Cerebral Vessels." *Guy's Hosp. Reports*, 1859, **v**, 281.

[40] Hanot, V. "Anévrysme artériel de la base du cerveau; rupture; épanchement sanguin dans la ventricle moyenne," *Bull. de la Soc. Anat.*, Paris, 1872, **17**, 257.

[41] Hare, C. J. "Aneurysm of Left Posterior Communicating Cerebral Artery Causing by its Pressure Paralysis of the Motor Oculi of the Same Side," *Trans. Path. Soc. Lond.*, 1848-50, **2**, 169.

[42] Harris, S. T. "A Case of Aneurysm of the Anterior Cerebral Artery Causing Compression of the Optic Nerves and Chiasma," *Brit. Journ. Ophthal.*, 1928, **12**, 15.

[43] Henneberg, R. "Ueber Gehirncysticerkose," *Berl. Charité-Annal.*, 1906, **30**, 214.

[44] Holmes, T. "Aneurism of the Internal Carotid Artery in the Cavernous Sinus," *Trans. Path. Soc*, London, 1861, **12**, 61.

[45] Humble, W. E. "Intracranial Aneurysm," *Lancet*, 1875, **2**, 489.

[46] Hutchinson, J., Jr. "A Case of Ulcerative Endocarditis; Aneurysm Pressing on Optic Commissure; Distension of Optic Nerve Sheaths; Amaurosis; Retinal Changes," *Trans. Ophthal. Soc.*, 1889, **9**, 152.

[47] Jefferson, G. "The Value of Radiology in Neuro-Surgery," *Proc. Roy. Soc. Med.*, July, 1936, **29**. (Section of Radiology, pp. 47-50.)

[48] Kennedy, F. "A Further Note on the Diagnostic Value of Retrobulbar Neuritis in Expanding Lesions of the Frontal Lobes. A Report of this Syndrome in a Case of Aneurysm of the Right Internal Carotid Artery," *Journ. Amer. Med. Assoc.*, 1916, **67**, 1361.

[49] Kirby, D. B. "Aneurysm of the Intracranial Portion of the Internal Carotid Artery," *Amer. Journ. Ophthal.*, 1924, **7**, 577.

[50] Kummell, R. "Zur Kenntnis der Geschwulste der Hypophysengegend," *Muench. Med. Wochenschr.*, 1911, **58**, 1293.

[51] Lebert, H. "Ueber die Aneurysmen der Hirnarterien," *Berl. klin. Wochenschr*, 1866, 209.

[52] Lodge, S. D., Walker, G. F., and Stewart, M. S. "Aneurysm of the Left Internal Carotid Artery Simulating a Pituitary Tumour," *Brit. Med. Journ.*, 1927, **2**, 1179.

[53] McKendree, C. A., and Doshay, L. J. "Visual Disturbances, of Obscure Ætiology, Produced by Focal Intracranial Lesions Implicating the Optic Nerve," *Bull. New York Neurol. Inst.*, 1936, **5**, 223.

[54] McKinney, S. McD., Acree, T., and Soltz, S. E. "The Syndrome of Unruptured Aneurysm of the Intracranial Portion of the Internal Carotid Artery," *Bull. New York Neurol. Inst.*, 1936, **5**, 247.

[55] Moore, R. F. "Medical Ophthalmology," London, 1925, p. 92.

[56] Nebel, D. "Observatio duorum aneurysmatorum rariorum, quorum alterum ex aortæ, alterum ex arteria corporis callosi ortum est." Inaug. Dissert. Heidelberg, 1834.

[57] Noiszewski. Quoted by Wildbrand and Saenger.

[58] Nunneley, T. "Circumscribed False Aneurysm of the Cerebral Portion of the Left Internal Carotid Artery," *Path. Trans.*, 1859, **11**, 8.

[59] Ogle. "On Morbid Growths of the Brain, &c. Case 247," *Brit. and For. Med. Chir. Rev.*, 1865, **36**, 494.

[60] Packard, M., and Zabriskie. "Basal Cerebral Hæmorrhages," *Journ. Amer. Med. Assoc.*, 1925, **85**, 1633.

[61] Patterson, A. "Aneurysm of the Left Internal Carotid Artery," *Edin. Med. Journ.*, 1859, **4**, 722.

[62] Peacock, T. B. "Intracranial Aneurysm," *St. Thomas's Hosp. Rep.*, 1876, **7**, 119 and 317.

[63] Pfingst, A. O., and Spurling, R. G. "The Role of Intracranial Aneurysms in the Production of Ocular Palsies," *Trans. Amer. Ophth. Soc.*, 1929, **27**, 227.

[64] Posey, W. C. "The Ophthalmic Record," 1911, p. 200.

[65] Reinhardt, A. "Ueber Hirnarterienaneurysmen und ihre Folgen," *Mitteil a. d. Grenzgeb. d. Med. u. Chir.*, 1913, **26**, 432.

[66] Rice, D. "Cerebral Aneurysm of Remarkable Size," *Journ. Ment. Sci.*, 1904, **50**, 305.

[67] Roe, H. "Aneurysm of the Anterior Cerebral Artery," *Proc. Path. Soc. Lond.*, 1850-52, **3**, 46.

[68] Sandford, H. S., Craig, W. McK., and Wagener, H. P. "An Unusual Chiasmal Lesion and its Operative Treatment," *Proc. Staff Meetings, Mayo Clinic*, 1936. **10**, 721.

[69] Schmidt, M. "Intracranial Aneurysms," *Brain*, 1930, **53**, 489.

[70] Schmidt-Rimpler. Aertzlicher Verein zu Marburg. *Berl. klin. Wochenschr.*, 1883, **20**, 353.

[71] Shannon, J. R. "A Case of Aneurysm of the Internal Carotid Artery (Intracranial Portion) and its Effect upon the Patient's Vision." *Arch. Ophth.*, 1917, **46**, 518.

[72] Sjoqvist, O. "Ueber intrakranielle Aneurysmen der Arteria Carotis und deren Beziehung zur ophthalmoplegischen Migrane," *Der Nervenarzt*, 1936, **9**, 233.

[73] Smith, G. Elliott. A Note on the Nervous Lesions produced Mechanically by Atheromatous Arteries." *Rev. Neurol. Psych.*, 1905, **3**, 182.

[74] Smith, R. W. "Multilocular Aneurysm of the Base of the Brain." *Dublin Journ. Med. Sci.*, 1844, **26**, 507.

[75] Sosman, M. C., and Vogt, E. C. "Aneurysms of the Internal Carotid Artery and the Circle of Willis, from a Roentgenological Viewpoint." *Amer. Journ. Roentg.*, 1926, **15**, 122.

[76] Spurgin, T. "A Case of Aneurysm of the Anterior Cerebral Artery." *Lond. Med. Repos.*, 1825, **3**. 443.

[77] Squire, H. "True Aneurysm of the Left Posterior Cerebral Artery." *Trans. Path. Soc. Lond.*, 1857, **8**, 166.

[78] Stilling. "Blindheit in Folge eines die Sehnerven comprimirenden Geschwulst." *Zeit. f. d. Ophth.*, 1833, **3**, 465.

[79] Symonds, C. P. "Contributions to the Clinical Study of Intracranial Aneurysms." Guy's Hosp. Reports, 1923, 73, 139.

[80] Symonds, C. P. Private Communication.

[81] Taylor, A. Quoted by McKendree and Doshay.

[82] Traquair, H. M. "An Introduction to Perimetry," London, 1931.

[83] Trevani, E. "Ein als parasellarer Tumor, operiertes Aneurysma der Arteria Carotis interna." *Deut. Zeit. f. Chir.*, 1932, **237**, 534.

[84] Tuthill, C. R. "Cerebral Aneurysms." *Arch. Path.*, 1933, **16**, 630.

[85] Van Bogaert, L., Helsmoortel, J., and Nyssen, R. "A propos d'un anévrysme suprasellaire." *Trans. 13th Congress Ophthal.*, 1929, 3, 156.

[86] Van der Byl "Aneurysm of the Posterior Cerebral Artery." *Trans. Path. Soc , Lond.*, 1856, **7**, 129.

[87] De Vet, A. C., and Zeckel, A. "Aneurysma van de Arteria Carotis interna. *Ned. Tijdschr. v. Geneesk.*, 1937, **81**, 4145.

[88] Wakeley, C. P. G. "The Surgery of the Parapituitary Region," *Med. Press and Circular*, 1937, **194**, 337.

[89] Wildbrand, H., and Saenger, A. "Die Neurologie des Auges." **6** and **7**, 1915, 1917.

[90] Wood, J. "Aneurysm of the Left Middle Cerebral Artery," *Trans. Path. Soc., Lond.*, 1868, **19**, 102.

[91] Zollinger, R., and Cutler, E. C. "Aneurysm of the Internal Carotid Artery." *Arch. Neurol. Psych.*, 1933, **30**, 607.

OBSERVATIONS ON DYSTROPHIA MYOTONICA.

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SUMMARY.

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OBSERVATIONS.

The present report includes the results of examinations of 57 families in which one or several members suffered from dystrophia myotonica.

	Male	Female	Total
Severe cases	61	26	87
Milder cases	15	25	40
Suspicious cases	69	76	145
Slightly suspicious cases ..	26	34	60
	171	161	332

In addition twenty male members and nine female members of these families whom it was not possible to examine were said to be affected with dystrophia myotonica. It is probable that these cases were severely affected, as mild symptoms would have remained unobserved.

The above figures show that severe degrees of dystrophia myotonica were more frequently observed in members of the male sex, but the higher number of females who were slightly affected, or presented suspicious signs, make it probable that females are affected with the taint of this disease as often as males, although the signs do not develop in the same degree.

A sharp differentiation between severe and milder cases cannot be made. I have called those cases "severe" in which myotonia, wasting and weakness were marked, but even some of those affected in pronounced degree did not feel much disability and were still at work. It was doubtful whether other cases should be called "mildly affected" or "suspicious" cases.

Five families were Jewish, the other families were British or German.

Myotonia.—The characteristic myotonia after active movements could not be observed in every case, not even in every severely affected case, although it became conspicuous on mechanical excitation. This difference between active movements and mechanical excitation was observed in six cases.

In several other severe cases myotonia on active movements was present in slight degree only, but was very marked on mechanical excitation. In many mild cases myotonia was very conspicuous on mechanical excitation, but was not observed on active movements. But although myotonia on active movements was not found in these persons, it probably was not completely absent, as several of them reported that they felt stiffness in their hands at certain times. In one mild case myotonia was present on active movements, but was very feeble on mechanical excitation.

These results demonstrate that the examination by mechanical excitation is often a more valuable test than examination by active movements.

A striking variability in myotonia was observed in one patient; as he was an in-patient in a hospital there was the opportunity of examining him repeatedly. Myotonia was very conspicuous on certain days, but was completely absent on other days. As far as could be determined this variability did not depend on the temperature of the air. It is well known that myotonia comes on in cold much more than in warm weather. Another patient reported that stiffness in his limbs disappeared after movement, a fact mentioned by many patients and frequently observed on examination. He stated further that stiffness was much worse on the day following unusually prolonged exercise—for example, on the day after he had played tennis for more than one hour. In one severe case a remarkable disturbance on active movements was observed; when he brought his arms up, or when he bent his forearms or straightened his fingers, these movements were done in the well-known slow way, but at certain intervals clonic jerks interrupted the slow movements for a few seconds. When the intended movement was performed his fingers and the flexor surface of his hands sweated profusely. A brother of this patient also suffered from dystrophia myotonica, but this unusual disturbance was not seen in his case.

The myotonic reaction on mechanical excitation was usually most conspicuous in the tongue and in the small muscles of the hand, but was not confined to these muscles. In many patients who could be examined in bed myotonia was observed in nearly all striated muscles, probably more often in the extensors of the forearm than in the flexors.

Muscular wasting.—Some authors have found that certain muscles are especially affected in dystrophia myotonica, viz. the facial muscles, sternomastoids, brachio-radialis and small muscles of the hands, while other muscles, especially those of the shoulder-girdle and of the pelvic-girdle, remain more or less unaffected. But no definite rule can be formulated as to which are most affected. No wasting of the facial muscles was found in two definite cases. The sternomastoids were unaffected in five cases, all of which occurred in the same family, and the brachio-radialis was not wasted in several severe cases.

A general wasting of the forearms was observed in a case in which the brachio-radialis was not more affected than other muscles. Neither the hand muscles, forearms nor arms were wasted in one severe case, but the sternomastoids as well as the facial muscles were atrophied and the lower limbs were weak; she walked with typical stepping gait and myotonia as well as cataract was well developed. No wasting of his limbs was observed in one case when aged 27 years, but seven months later slight wasting of his left hypothenar, and doubtful wasting of his left thenar, eminence were observed.

One man presented definite affection of the muscles of his shoulder and pelvic girdles. His scapulæ were winged and he had great difficulty in getting up from a lying position without using his hands, like a case of myopathy. Slight atrophy only was observed in his sternomastoids, brachio-radialis, and the small muscles of his left hand and in all muscles of his lower limbs. This case has already been mentioned in connection with the variability of the mechanical myotonic reaction in his limbs.

A conspicuous weakness in the pelvic-girdle was found in a patient (Mrs. C. J., 1 (ii) 6)[1] who had much difficulty in getting up from a sitting position but in whom other signs of dystrophia myotonica were not marked.

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[1] Where family trees are published the position in the family of the patient referred to is indicated in this manner.

In another case some muscles of the shoulder-girdle were weak and the scapulæ were winged, although neither wasting nor weakness were very marked in his upper limbs; myotonia was especially conspicuous in his tongue and in his hands.

These cases demonstrate that no definite rule can be given as to which muscles waste early, although certainly in the majority of cases the temporals, cheeks, sternomastoids and small muscles of the hands are more or less wasted and weak.

In greatly wasted muscles the myotonic reaction was usually absent. In one case in which all the muscles of the limbs were greatly wasted and paralysed, in only a small part of the left thenar group could a myotonic reaction be produced by mechanical excitation; this patient reported, however, that she had felt the characteristic stiffness on active movements when her disease began many years ago.

No person suffering from definite myotonia but perfectly free from wasting was examined. The diagnosis of "Thomsen's Disease" was therefore not made, but in four patients who were affected with myotonia, wasting could be observed in a few muscles only.

In one man, aged 34, a case of myotonia dating from infancy, hypertrophy was observed in the upper and lower limbs, especially in the deltoids, trapezii, biceps and quadriceps on both sides, while there was slight wasting in the facial muscles and sternomastoids and probably also in the peronei. Strength was everywhere poor, though he stated that in his boyhood he had been exceptionally strong. His brother was similarly affected; he suffered from stiffness in his limbs and sometimes cramp in his neck muscles, but on examination myotonia and wasting were only slight though there was marked weakness of many muscles.

Asymmetry of the muscular wasting was observed occasionally. In Albert B., who was observed at the age of 20, the cheeks were definitely thin, the left brachio-radialis was smaller than the right, the left thenar muscles were flatter than the right, and the temporals were suspicious of early wasting. In Arthur B. (aged 26), in whom myotonia was present from infancy, the temporals were slightly wasted, the cheeks were a little thin, the left sternomastoid was definitely wasted by comparison with the right, and the lateral parts of both thenar eminences were also slightly atrophied. In another case dating from infancy, the temporal muscles had been wasted for about fifteen years. His cheeks were thin, but were not-definitely pathological. His left thenar eminence was flatter than his right, the proximal end of his left supinator appeared to be thinner than his right, and all muscles in the upper and lower limbs were small. His obliqui abdominis also appeared to be wasted.

Tendon reflexes were often absent in mild cases as well as in severe. They were preserved, however, or only one or more absent, in some severe cases. For example, in a man aged 56, who was very severely affected, the left supinator reflex only was absent, and in another severe case the right knee-jerk and both ankle-jerks were present.

Cataract.—It is noteworthy that cataract, a sign observed so often in cases of dystrophia myotonica, was absent in the four patients in whom signs of muscular wasting were observed in an unusually slight degree, whilst myotonia was marked. In another patient (12 (iii) 4) who was free from cataract, myotonia as well as intellectual defects were marked, whereas wasting of muscles was slight. The muscles in his thighs, as well as his deltoids, were especially well developed and were perhaps pseudo-hypertrophic, as their strength seemed to be rather poor compared with their volume.

One mild case (9 (c) (iii) (2) 4) is of interest in this connection. Signs of dystrophia myotonica were observed in her mother, her brother and her two sisters. Myotonia was conspicuous in her tongue and her hands, and there was slight atrophy in her right thumb and definite weakness on closing her eyes and blowing out her cheeks. No cataract was found at the time of the first examination, but fifteen months later Mr. Goulden observed a few suspicious green crystals in the anterior part of her lenses. Her mother had been operated on for cataract at the age of 44, and in her brother and in two sisters evidence of cataract had been observed on slit-lamp examination.

Cataract presenting the peculiarities which are generally regarded as characteristic of dystrophia myotonica [13] was observed in several brothers and sisters of patients suffering from this disease, in whom only suggestive evidence of muscular disturbances could be found. As all healthy siblings were not submitted to a slit-lamp examination, it is impossible to give the proportion in which cataract was the only definite sign.

In two "healthy" mothers of patients cataract was observed on slit-lamp examination. In one no other suspicious sign was observed, but in the other, besides cataract which produced no trouble, there was a suspicious myotonic reaction to mechanical excitation of the thenar muscles, slight wasting of the facial muscles and on electrical examination "the thumb muscles of both hands required a strong faradic current to elicit a contraction. There was a tendency to a slow, sluggish response to the interrupted galvanic current and a suggestion of hypertonicity to the constant galvanic current."

It is of interest that in several cases alterations in the lenses were observed which were suspicious of the typical cataract, but which were so slight that the ophthalmic surgeon conld not give a definite opinion. One case of this kind was mentioned on page 502 (9 (c) (iii) (2) 4). Two other cases had only suspicious muscular abnormalities.

(1) Eileen D., aged 18, the cousin of a severe case, had been mentally deficient since infancy. There was no myotonia, but definite wasting of the right sternomastoid and doubtful atrophy of the left brachio-radialis and left thenar muscles. Examination by slit-lamp gave "a few fine sparkling angular opacities, throughout the lens cortex in each eye, very few glistening coloured spots. suspicious of the commencement of cataract."

(2) Arthur G. R. (1 (iii) (4) 5), aged 21, whose father, brothers and sisters suffer from dystrophia myotonica was mentally very defective. There was a suspicious myotonic reaction to mechanical excitation of the tongue and thenar muscles, with slight wasting of the temporals, doubtful wasting of the right peroneal muscles, and weakness on blowing out the cheeks and in dorsal flexion of the feet. Examination by slit-lamp gave "Fine odd opacities in both nuclei, a congenital condition commonly found. A few angular opacities in the cortex of both lenses, which are probably due to myotonia, but require confirmation at a later date."

These cases indicate that some siblings may show suspicious signs of cataract as well as of the muscular affection, but a definite diagnosis of dystrophia myotonica could not be made.

Testicular atrophy.—Like other authors I observed small and soft testes in many severe and mild cases, and many of my patients also reported disturbance of sexual power. Two patients, however, became fathers in advanced stages of dystrophia myotonica. F. (1 (ii) 4) at the age of 36 was an in-patient at the National Hospital, where he was found to be severely affected with this disease. His seventh and his eighth children were born when he was aged 37 and 39. John (1 (ii) 5), his step-brother, was an in-patient at the National Hospital at the age of 31. His testes were soft, but he became a father in the same year and again eleven years later. So-called secondary sexual characters were poorly developed in the majority of definite cases.

Baldness was often present, more frequently in male patients than in female; it started usually at the sides of the forehead, but its diagnostic value as a sign of dystrophia myotonica is not important.

Enlargement of the thyroid does not seem to be very uncommon. It was present in six more or less severe female cases and in two severe male cases. One severe female case is reported to have had a goitre at the time when she began to suffer from dystrophia myotonica. Thyroid enlargement was also seen in several suspicious cases.

CLASSIFICATION OF CASES.

I have called "suspicious" and "slightly suspicious" cases all relatives of definite cases in whom only one or other sign of dystrophia myotonica was observed.

In many of these cases typical myotonic contraction of muscles was found on mechanical excitation, especially in the tongue and thenar or hypothenar muscles.

It is well known that the degree of reaction to mechanical excitation is not the same in every normal person. In some the thenar muscles contract after mechanical excitation up to complete opposition of the thumb, but the contraction comes on quickly, not slowly as in a typical case of dystrophia myotonica, and relaxation, also, is less delayed than in this disease.

In a certain number of persons in affected families the contraction of the thenar and hypothenar muscles after mechanical excitation occurred at a rate more or less mid-way, so that it was impossible to decide whether the contraction was normal or pathological.

In the majority of "suspicious cases" there was more or less marked wasting of muscles, particularly in the facial, sternomastoids and thenar muscles and weakness of the dorsiflexors of the ankles; in some cases also there was general wasting in the neck and upper and lower limbs.

It is well known that the temporal muscles and cheeks are wasted in many healthy persons in old age, as well as in young persons who suffer from a wasting disease, such as cancer or tuberculosis of the lungs, but only as an exception have I observed wasted facial muscles in healthy young persons.

The following two patients, cousins of typical cases but not themselves suffering from dystrophia myotonica, showed a myotonic reaction to mechanical excitation:—

(1) Clara S. (9 (b) (ii) 2), aged 53, had slight wasting of the temporals and a definite myotonic reaction in her tongue and a suspicion of it in the thenar muscles. She had a poor grip and the right triceps reflex was absent.

(2) Mary F. (9 (b) (ii) 6), her sister, aged 42, suffered from "neuritis" in her upper limbs eight years ago. On examination there was slight wasting in

her temporals, a definite myotonic reaction in her tongue, and her thenar muscles gave a response suspicious of the myotonic reaction on mechanical excitation. Her grip was poor.

Wasting of a sternomastoid in persons not suffering from dystrophia myotonica is demonstrated by two cases :—

(1) Herbert Geo. (9 (a) (ii) 3), the cousin of typical cases of dystrophia myotonica, aged 44, feels healthy and is at work. The right sternomastoid was definitely wasted (fig. 1), the left brachio-radialis not so well developed as the right, which was also not quite normal. Probably there was some weakness on shutting the eyes and a certain degree of hypertrophy of the flexors in both forearms. These observations were confirmed by Dr. Riddoch.

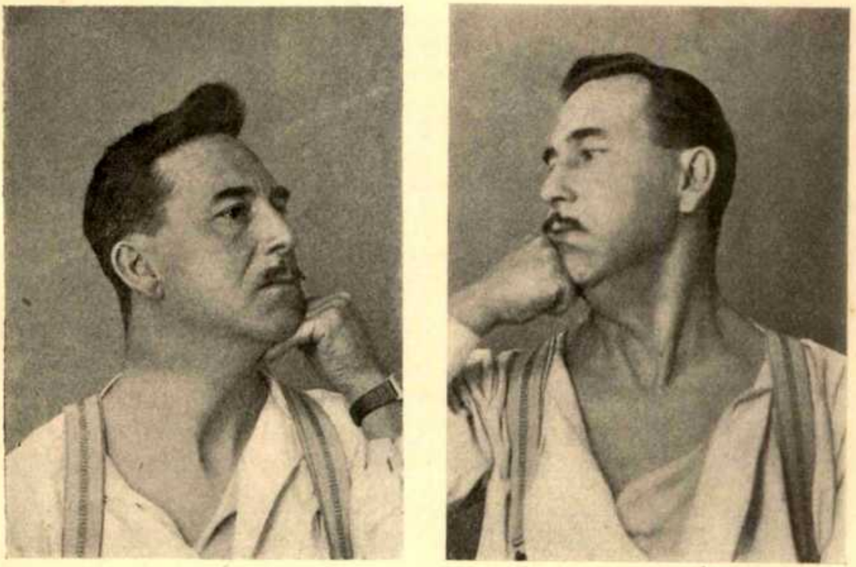


FIG. 1.

(2) Mrs. D., aged 76, had one son and several grandchildren suffering from dystrophia myotonica. She felt and looked perfectly healthy. The left sternomastoid was, however, wasted and the left thenar muscles slightly so. Occasionally there was myotonic reaction to mechanical excitation in the left hypothenar muscles. The supinator and triceps reflexes were absent. On slit-lamp examination no cataract was observed.

Wasting of the facial muscles is illustrated by the following cases :—

(1) Alfred T. (9 (c) (ii) 3), aged 45, whose brother and sister suffer from dystrophia myotonica, had complained of cramps in his hands and lower limbs

for fifteen years. His haggard face was typical of dystrophia myotonica; his cheeks are thin and the temporals wasted. There is probably weakness on blowing out his cheeks and the left thenar muscles are flatter than normal; there is doubtful myotonic reaction to mechanical excitation in the left trapezius and the right triceps. The muscles in the lower limbs are fairly thin. There is a typical early cataract.

(2) Frederick J. D. (10 (iv) 3) was aged 22. A paternal uncle as well as a sister suffer from dystrophia myotonica. He feels perfectly healthy. On examination definite wasting of the temporals was found and his face was thin. There is a suspicion of myotonic reaction to mechanical excitation in the extensors of both forearms and a weakness of dorsal flexion of both feet. Otherwise he is normal in every way and has no cataract.

As an example of wasting of the small muscles of the hand, especially often observed in suspicious cases, I may mention Mrs. G. (2 (ii) 10), aged 87, many of whose nephews and nieces suffer from dystrophia myotonica (*vide* Greenfield [14]). Her memory is disturbed, probably as a result of old age, but her behaviour is normal. She has suffered from cataract for many years. There is definite wasting in both thenar muscles, but no myotonic reaction. Several similar cases were observed.

Weakness of muscles was often seen in "suspicious cases," especially of those affected in definite cases of dystrophia myotonica, for example, in the facial muscles, the flexors of the fingers and the dorsiflexors of the feet. One of the "suspicious cases," the brother of three sisters suffering from dystrophia myotonica (Family Hur.), was free from definite signs of the disease, but he could not blow out his cheeks properly. It is noteworthy that in some mildly affected, as well as in some "suspicious," cases the lateral part of the thenar group only was wasted, whilst the inner part seemed to be normal. One case of this kind is the following:—

Thomas B., aged 24, whose brother had suffered from myotonic disturbance since infancy but in whom only a few muscles were wasted, felt healthy but he reported that he could not play a trumpet as long as other members of his orchestra because the muscles of his mouth tired quickly, and his hands also tired rapidly when playing the piano. On examination there was slight wasting of the left abductor pollicis and a suspicion of general wasting of the forearms. The left sternomastoid was probably not so well developed as the right and the grip was not strong. There was a definite myotonic reaction to mechanical excitation in the hypothenar muscles.

A similar condition was found in other cases.

Electrical Reaction of Muscles.

The reaction to faradic and galvanic currents gave valuable results in "suspicious" and "slightly suspicious" cases. Dr. Bailey was kind enough to make these examinations.

The electrical myotonic reaction described by Erb [9] is generally regarded as characteristic of myotonia congenita (Thomsen's disease) and dystrophia myotonica. It has also been observed in a few cases of another nature by Hoffmann and by Kramer [16] and by Falta [11]. Dr. Martin observed such a case in the National Hospital (S.Mc.L.), probably as a result of thyroid deficiency; she had a rough dry skin and myotonic reactions on electrical excitation, mechanical excitation and active movements, which completely disappeared after treatment with thyroid extract. Such cases can be disregarded, as the characteristic signs of endocrine deficiency are present.

Four cases in which by other methods of testing only a few suspicious signs of dystrophia myotonica were found, but in which there was a definite myotonic reaction on electrical examination, may be mentioned.

(1) Catherine May D., aged 26, is a nurse and feels healthy. A brother and sister of her father suffered from dystrophia myotonica. On examination there was found slight myotonic reaction in her tongue and slight wasting in the lateral part of both thenar muscles. The temporals were slightly wasted and the grip was poor. No cataract was found on slit-lamp examination. On electrical examination "the right and left opponens pollicis were stimulated by means of the interrupted faradic and galvanic currents. Faradic response was obtained with an extremely small current incapable of stimulating a normal muscle. Galvanic response was obtained with 2 ma. of current, whereas in a normal muscle 5-6 ma. were necessary. The galvanic response was also obtained at the make and break of the current with 4 ma. The continuous uninterrupted current tetanized both muscles with 5 ma. The above findings show definite hyper-excitability to both the faradic and galvanic currents, i.e. *a myotonic reaction.*"

(2) Ernest G. L., aged 26, a student whose maternal uncle suffered from dystrophia myotonica, feels healthy. The left thenar and both hypothenar muscles gave suspicious myotonic reactions to mechanical excitation. There was slight wasting of the left abductor pollicis and the temporals were slightly atrophied. There was a possible weakness in blowing out the cheeks. On electrical examination, "the thenar and hypothenar muscles of both sides responded to a weak faradic current, insufficient to produce contraction in a normal muscle. The muscles also contracted well to an interrupted galvanic current of 6 ma. A contraction was obtained to make and break of current at 10 ma. in the right opponens pollicis. There was a tendency for the

constant current to tetanize the muscle. The evidence is in favour of hyperexcitability of muscle-fibres, *therefore of an early myotonic reaction.* There was slight wasting of the abductor pollicis of the left side, but its electrical reaction still showed some hyperexcitability."

(3) In John Edward M., aged 14, whose brother, aged 32, suffers from dystrophia myotonica and whose mother, another brother and a sister are affected with typical cataract, there is a doubtful wasting in the temporals; otherwise he was normal. There is no cataract. On electrical examination, "the left thumb is normal. In the right thumb the faradic response is normal, but with an interrupted galvanic current the response of the abductor and opponens pollicis is sluggish in character, the relaxation being slow, possibly due to tetany. With 6 ma. of current a contraction in both these muscles was elicited at the make and break of the current. This was not the case in the left thumb. No one of these muscles was wholly tetanized with the constant current."

(4) Charles D. (6 (iii) (1) 3), aged 34, whose mother, brother and sister suffer from dystrophia myotonica, showed a myotonic reaction in the tongue, slight wasting in the temporals and both tibialis anticus muscles, and dropping of both upper lids. There was weakness in the peroneal muscles; the closing of the eyes was also probably weak; the supinator and triceps reflexes were absent. On electrical examination slight tetanic contraction of the left side of the tongue was observed with 2½ ma. current.

In many other cases, both of definite and suspicious character, the electrical reactions were abnormal. Though in several suspicious cases no abnormality was found, electrical testing must be regarded as a valuable method of investigation in all doubtful cases.

In this connection a case reported by Babonneix [2] is remarkable. He observed a myotonic electrical reaction in a man who was absolutely free from other signs of myotonia, but who was a brother of a patient with Thomsen's disease.

It would have been valuable if the results of electrical, and still more of mechanical, stimulation could have been recorded in a graphic manner, but unfortunately this was impossible at the time of examination.

AGE OF ONSET OF DYSTROPHIA MYOTONICA.

It has been often stated that dystrophia myotonica starts after the age of 20 or 30, whilst Thomsen's disease is an inborn affection. My own observations demonstrate, however, that dystrophia myotonica often begins in early infancy.

John Kenneth R. (1 (iii), (5) 4), a boy of 3½ years, the son of a severe case of dystrophia myotonica, gave definite myotonic reactions to mechanical excitation in the thenar and hypothenar muscles.

Anita R., aged 6¾ years, the sister of a severe case, showed a definite myotonic reaction of the tongue and probably also of the right thenar muscles, and weakness of the facial muscles.

In the following patients, most of whom suffered severely from dystrophia myotonica, symptoms of the disease had been noticed in early life:—

Otto B. (8 (ii) 3), aged 34, felt stiffness in his hands at 8.

Bernard B. (8 (iii) (2) 1), aged 18, noticed stiffness in his hands at 12; his mother, who had observed the development of the disease in his father, reported that her son's voice became raucous like his father's when he was only 7 years of age.

Leslie W. (7 (iii) 5), aged 13, had, when examined at the age of 9, facial weakness, defective speech, stepping gait and enlarged muscles.

In seventeen other patients who were examined symptoms of the disease had been noticed during childhood or adolescence.

I have observed also in numerous relatives of patients definite signs of the affection, such as myotonia on mechanical excitation, and in some of them also on active movements, slight wasting or weakness of muscles, absence of one or other of the tendon reflexes, or typical early cataract which produced no disturbance of eyesight, in persons unaware of any symptoms of the disease. In such cases it is uncertain when these abnormalities first appeared.

I examined also many children of patients suffering from dystrophia myotonica in whom one sign or other of the disease was present, but whether, and at what time of life, they will suffer from any disability is at present unknown. Several patients affected with definite signs of dystrophia myotonica had been mentally defective since infancy. As they had not been specially examined in infancy we do not know when these signs first appeared.

These patients who had symptoms characteristic of dystrophia myotonica in childhood, as well as the children in whom I observed these signs, prove that dystrophia myotonica certainly often starts at quite an early age.

Observations on Sibships in which One Member at least was a Definite Case of Dystrophia Myotonica.

(1) *Number of Affected, Suspicious and Healthy Persons in these Sibships.*

I observed one or more definite cases of dystrophia myotonica in 69 sibships in 55 families. Two families which were examined later have not been considered in the following statistics. Eighty-four miscarriages and deaths in infancy were reported in these 69 sibships and 59 persons had died in later life. Nothing was known of 54 members who had grown up. In all, 215 persons were examined in these 69 sibships.

The results are summarized below:—

	Male	Female
Severely affected	53	35
Mildly affected	19	22
Suspicious cases	32	29
Slightly suspicious cases	8	6
Healthy cases	7	4
	119	96

An exact statistical examination of the disease in the affected sibships is not possible at present, as many members were not examined, and among those examined 75, or 35 per cent., presented only suspicious or slightly suspicious signs and 11 no suspicious signs at all. A considerable advance in this direction, however, could be made if more objective and exact methods of examination could be applied to suspicious and "healthy" cases.

(2) *The relation of birth order to severity of signs.*

In order to discover whether the incidence or severity of the disease had any relation to a patient's position in the family, I asked Dr. L. S. Penrose to analyse the results of my examinations up to June, 1936. He has compiled Table I and has given the following report:—

"We find that the severe cases are less frequently found at the beginning of the family than is to be expected. This conclusion applies also to the milder cases. Similarly, there are more severe and milder cases than are to be expected if we take the birth rank from the fifth to the twentieth. This effect is not very marked and it is possible that it may be accounted for by the fact that those severe cases which occur early in the family died before one had an opportunity to examine them. Thus the group of 'died' and 'miscarriages' shows a marked excess of the first-born above the expectation (22 against 14·87). The figures certainly suggest that severe cases tend to occur towards the end of a family, but no definite conclusion can be arrived at. There may be a main gene responsible for dystrophia myotonica and numerous modifying influences, one of which may be associated with birth order."

TABLE I.

Birth rank	N		U_1		U_2		S_1		S_2		A_1		A_2		Total	
	T.	Exp.	T	Exp.	T.	Exp.	T.	Exp.	T.	Exp.	T	Exp.	T.	Exp.	T.	Exp.
1	2	1·14	5	4 86	22	14·87	1	1·44	5	8·58	7	8·09	8	11·02	50	50·00
2	—	1·14	7	4·86	14	14·87	2	1·44	9	8·58	9	8·09	9	11·02	50	50·00
3	—	0·14	3	5·20	15	13·37	2	0·94	11	7·24	7	7·59	4	7·54	42	42·02
4	—	0·14	5	4·53	13	12·04	—	0·94	5	5·91	6	6·59	7	5·86	36	36·01
5	—	0·14	2	4·28	13	10·97	—	0·94	7	5·45	7	6·37	4	4·86	33	33 01
6	—	0·14	4	3·75	6	9·54	2	0·94	2	3·89	5	4·09	7	3·66	26	26·01
7	—	0·14	3	2·86	7	7·22	1	0·60	1	2·05	2	2 97	4	2·10	18	17·94
8	—	0·14	2	2·13	8	5·49	—	0·57	—	2·05	3	2·94	2	1·67	15	14·99
9	—	0·14	2	1·44	3	3·67	—	0·35	1	0·84	1	0·71	1	0·84	8	7·99
10	—	0·14	—	1·33	2	2·67	—	0·35	1	0·84	1	0·27	2	0·39	6	5·99
11	1	0·14	1	1·23	1	2·47	—	0·05	2	0 74	—	0·07	—	0·29	5	4·99
12	—	0·05	1	0·68	1	1·74	—	0·05	1	0·29	—	0·07	—	0·11	3	2·99
13	—	0·05	1	0·68	2	1·74	—	0·05	—	0·29	—	0·07	—	0·11	3	2·99
14	—	0·05	1	0·68	1	1·74	—	0·05	—	0·29	—	0·07	1	0·11	3	2·99
15	—	0·05	2	0·11	—	1·39	—	0·05	—	0·29	—	0·00	—	0·11	2	2·00
16	—	0·05	—	0·11	—	1·39	1	0·05	1	0·29	—	0·00	—	0·11	2	2·00
17	—	0·05	—	0 05	—	0·70	—	0·05	1	0·10	—	0·00	—	0 05	1	1·00
18	1	0·05	—	0·05	—	0·70	—	0·05	—	0·10	—	0·00	—	0·05	1	1·00
19	—	0·05	—	0·05	—	0·70	—	0·05	1	0·10	—	0·00	—	0·05	1	1·00
20	—	0·05	—	0 05	—	0·70	—	0 05	—	0·10	—	0·00	1	0·05	1	1·00
Total	4	3·99	39	38·93	108	107·98	9	9·01	48	48·02	48	47·99	50	50·00	306	305·92

N = normal.
U_1 = not examined.
U_2 = died (this includes miscarriages)
S_1 = suspicious.
S_2 = slightly suspicious.
A_1 = mild affection.
A_2 = severe affection.

The most affected member of the sibship was :—

The youngest in twenty-six sibships of the following number of siblings: 9, 10, 6, 6, 5, 6, 6, 9, 20 (?), 6, 5, 7, 4, 2, 3, 2, 3, 2, 3, 2, 2, unknown, 6, 4, 3 (?), 5, 3, 3.
The 10th in one sibship of 11.
,, 8th ,, ,, ,, ,, 11.
,, 7th ,, ,, ,, ,, 8.
,, 5th ,, ,, ,, ,, 11.
,, 4th ,, three sibships ,, 6, 8, 8.
,, 3rd ,, two ,, ,, 4 and 7.
,, 2nd ,, ,, ,, ,, 3 and 5.
,, 1st ,, eight ,, ,, 2, 2, 4, 4, 5, 6, 7, 8.

In six sibships several members were equally affected with severe signs.

The figures submitted to Dr. L. S. Penrose cannot be regarded as final, as in several of the sibships the younger members were still young, so that we have no present knowledge which member will eventually be the most affected.* In this connection a sibship may be mentioned (2 (iii) (8)) which was described by Greenfield in 1911 [14]. The youngest, aged 25, had no symptoms of dystrophia myotonica in 1910, but he was as seriously affected as the 10th, the 12th, and the 13th members of the sibship when I examined them in 1935.

In three other sibships, in whom the patient was the eldest, the youngest were respectively only 7, 11 and 14 years of age.

Probably the effect of birth order may be counterbalanced in some sibships by the influence of sex. As stated in the beginning of this paper, severe cases were observed more frequently in males than in females. The influence of sex may thus explain why in several sibships the youngest *male* member was most affected, while younger female members were less affected. As examples of this supposed influence of sex, the following sibships may be mentioned :—

(1) A patient, male, was the 10th of 11 ; the 11th, a female, was a definite but less severe case.

(2) A patient, male, was the 4th of 8 ; the 5th and the 6th, both male, had died; the 7th and the 8th, both female, were less seriously affected than the 4th.

(3) Karl S. (12 (ii) 4), male, was the 4th of 9 ; the 5th, female, was less affected ; the 9th, female, was unaffected ; the 6th, 7th and 8th had died in youth or in infancy.

The influence of birth order is best seen in sibships of which numerous members could be examined and in which only the youngest was severely affected, e.g. Family T. (9).

Certainly an influence of birth order is not evident in all the sibships examined by other authors, but in several large sibships which have been recorded only the youngest members were severely affected. (Curschmann [6], Bramwell and Addis [4], Fleischer [10].

Observations on Fraternal Anticipation.

There is some dispute as to the occurrence of fraternal anticipation in mental diseases, i.e. that the disease tends to start at an earlier age in the younger members of a sibship than it does in the elder (A. S. Paterson [18]). As many persons feel perfectly healthy, although showing definite signs of dystrophia myotonica, we cannot always determine the age of onset. At present we can only compare the ages at which persons suffering from dystrophia myotonica began to present symptoms of the disease.

In spite of the numerous families at my disposal, I obtained useful information as to the time of appearance of muscular symptoms in the following eight families only. In these families 3, 3, 3, 2, 2, 2, 2, and 5 members were definite cases, most of them severely affected. A fraternal anticipation was observed in all, except in the last mentioned (the family S. 2).

(1) Family 8 (a) Klara R., aged 51, feels quite healthy: she had eye trouble at 48 and now presents typical signs of dystrophia myotonica.

(b) Paul B., aged 48: first had trouble in his hands at about 32 and with his eyesight at 46; signs of dystrophia myotonica were typical.

(c) Otto B., aged 34: weakness in his hands started in early infancy and myotonic disturbance in his hands at 8: there was mental enfeeblement for two years. Typical signs of dystrophia myotonica were observed on examination.

(2) Family 6 (a) Mrs. D., aged 58, does not complain of stiffness: she had eye trouble at 52 and an operation for cataract at 56. Definite slight signs of dystrophia myotonica were present in tongue and hands; no wasting was observed but the facial muscles were weak; the knee-jerks were absent.

(b) Robert G., aged 55, noticed loss of power in his lower limbs at 50. Typical myotonia was found in tongue and hands, with slight wasting of the left sternomastoid, forearm and peroneal muscles; the triceps reflex and ankle-jerks were absent; grip was poor. (He died a few months later with carcinoma of the lung.)

(c) Mrs. D., aged 49, had eye trouble at 46 and an operation for cataract at 49; she began to fall when walking and complained of weakness in the hands at 45; there was typical myotonia in tongue and hands; the sternomastoids were completely wasted and the thenars slightly; the upper and lower limbs were weak and she could only walk supported by others.

(3) (a) John McD., aged 26, felt stiffness in his hand at about 20; he had typical signs of dystrophia myotonica.

(b) Albert McD. (died at 17), noticed his hands stiff, probably for the first time at 10; he also had typical signs of dystrophia myotonica at 15.

(c) Eric McD., aged 15, came as a patient to the National Hospital in 1931 at the age of 10; he reported that stiffness started at 8; he had typical signs of dystrophia myotonica.

(4) (a) Irene B., aged 30. Weakness in legs started at 27, a goitre appeared at 26; this was a typical case of dystrophia myotonica.

(b) Cyril B., aged 24, had been mentally defective since infancy; at 24 there were severe signs of dystrophia myotonica.

(5) Family 9 (a) Frank, aged 34, was in good health up to the age of 24; cataract was observed in 1928 and definite sign of muscular disease at 34.

(b) Violet, aged 23, complained of general weakness at 21; walked badly at 20 and had difficulty in learning. She was a typical case of dystrophia myotonica.

(6) (a) J. de N., aged 56, a very severe case of dystrophia myotonica, observed a disturbance of the eyesight at 18 and muscular weakness at 20.

(b) Clara de N., aged 47, a very severe case of dystrophia myotonica, fell down in the street at 10 or 11 and had difficulty in getting up; she could not walk fast six months later.

(7) Family 1. (a) In Frederick T. A. R., aged 50, a severe case of dystrophia myotonica, general weakness started at the age of 30; he was an in-patient at the National Hospital, suffering from severe symptoms, at the age of 36.

(b) John (his step-brother) aged 44, a severe case of dystrophia myotonica, felt stiffness in his hands at the age of 24; he was an in-patient at the National Hospital, suffering with pronounced symptoms at the age of 31.

(8) Family 2 (iii) 8. (a) Charles, the seventh child, who died at 48; complained of weakness at 34.

(b) Letitia, the tenth child, aged 59, felt weakness at 33.

(c) Ellen, the twelfth child, aged 56, noticed weakness at 22.

(d) Laura, the thirteenth child, aged 55, felt weakness in infancy.

(e) Arthur, the fifteenth child, aged 50, noticed weakness at 32.

Thus fraternal anticipation seems to be common, but the number of cases so far available is too small to establish a definite rule.

HEREDITY OF DYSTROPHIA MYOTONICA.

Nearly all authors agree that dystrophia myotonica is an hereditary affection. My own observations were as follows:—

(1) Cases of dystrophia myotonica in two generations were found in thirteen families which I have examined.

(2) It was reported that one or several members of the preceding generation suffered from dystrophia myotonica in fourteen other families. In some of these families probably members of three or four generations were affected.

(3) In two other families typical cataract was seen in the mothers of patients suffering from dystrophia myotonica.

(4) In nine other families it was stated that a member of the preceding generation suffered from cataract.

(5) In fifteen cases no history of inheritance was available.

Like Boeters [3] I observed half-brothers and half-sisters affected in several families. In the families 1 and 3, the affected persons were descendants of the same father; in the descendants of Mrs. C. (R) 1 (ii) 6, the affected persons were children of the same mother. Percival D. had two affected children by his first wife, while both children by his second wife, both young boys, were suspicious cases.

The frequency with which dystrophia myotonica affects members of two generations as well as the repeatedly observed affection of half-brothers are in favour of dominant heredity.

Evidence in favour of recessive inheritance was observed very rarely in the families examined. Two patients were the children of first cousins. On the other hand in the family 9 (a) and (b), two men, Simon John T., junior, and Archibald M., were married to cousins of the T. family; but in their children only slightly suspicious signs of dystrophia myotonica were observed. Only one patient reported that both his father and mother suffered from cataract; in all other cases in which a history of cataract in the previous generation was obtained only the father *or* the mother was affected. In one sibship the mother was affected with cataract and had slightly suspicious signs of dystrophia myotonica. More or less suspicious signs were present in relatives of both parents.

TABLE II.

Parents	Children						Total
	U	N	S_1	S_2	A_1	A_2	
U	93 (48%)	4 (2%)	13 (7%)	38 (20%)	19 (10%)	26 (13%)	193
N	15 (42%)	1 (3%)	— —	16 (44%)	1 (3%)	3 (8%)	36
S_1	31 (53%)	5 (9%)	1 (2%)	14 (24%)	3 (5%)	4 (7%)	58
S_2	22 (18%)	16 (13%)	25 (21%)	32 (27%)	17 (14%)	8 (7%)	120
A_1	29 (35%)	4 (5%)	2 (2%)	22 (27%)	19 (23%)	6 (7%)	82
A_2	21 (44%)	— —	4 (8%)	14 (29%)	4 (8%)	5 (10%)	48

U = not examined.
N = normal.
S_1 = slightly suspicious.
S_2 = suspicious.
A_1 = mildly affected.
A_2 = severely affected.

Dr. L. S. Penrose was kind enough to examine my observations with reference to the relationship of disease in the parent to disease in the children. He drew up Table II and made the following conclusions:—

> "When the parents are normal about 11 per cent. of the children are affected; when the parent has suspicious signs about 16 or 17 per cent. of the children are affected; when a parent is affected about 26 per cent. of the children are affected. If we assume that the majority of the individuals called 'unknown' are normal and that many of the suspicious cases are also normal, this finding would be in keeping with the hypothesis of dominant inheritance, but in which more than one factor is involved. There may be a main 'gene' responsible for myotonia atrophica and numerous modifying influences, one of

> which may be associated with birth order. I do not think that the hypothesis of cytoplasmic inheritance which I suggested as a possible explanation of the great variety of forms is very probable, but I think it might be the only way of explaining the extreme rarity of normal individuals."

Fertility.—The number of children born of patients affected with dystrophia myotonica is small. I observed 29 male cases over 23 years of age who had no children. The wives of 18 male cases over 23 years of age had 88 pregnancies, but only 58 children were alive. Twenty-four female cases over 23 years of age had no family. Among 17 female cases over 23 years of age there had been 74 pregnancies; only 39 of the children were alive. Consequently 88 persons affected with dystrophia myotonica had only 97 living children. Among these children a certain number were severely affected mentally, so that they will not marry; other children were affected with "suspicious" signs when young, so that it is doubtful if they will become parents.

The following observations bear on the question whether dystrophia myotonica can be transmitted from previous generations through persons themselves unaffected.

(1) Mrs. L., aged 55, felt perfectly healthy and the only pathological signs I observed were slight wasting of temporals and inability to blow out her cheeks. A brother, who was examined at the National Hospital, was a severe case of dystrophia myotonica. E. G. L., her son, aged 26, presented slight but definite signs of the disease, especially on electrical examination.

(2) Mrs. M. (Family 9 b), aged 74, was healthy and showed no signs of dystrophia myotonica. In many of her children I observed the typical myotonic reaction and slight wasting of muscles. None felt ill or was suffering from dystrophia myotonica. Many cousins suffered from this disease; the father of these cousins was healthy up to his death at the age of 69, but his brother and his brother's son had slight evidence of the disease.

(3) William (2 (ii) 8) (Greenfield [14], 1911), was in good health at the age of 69, when examined by Greenfield. His mother and other relatives suffered from cataract. Many of his children suffered from dystrophia myotonica.

(4) William S. (2 (iii) (8) 3), the son of the above, was normal when examined by Greenfield and never suffered from signs of dystrophia myotonica. In his third child the temporal muscles were wasted, the left sternomastoid was smaller than the right and there was doubtful weakness on blowing out her cheeks.

(5) Sam W. (3 (ii) 18), was normal, but there were signs suspicious of dystrophia myotonica in his three children. His brother, Arthur, was a severe case of this disease.

Although none of these cases was absolutely conclusive, as neither slit-lamp nor electrical examination had been done in the healthy parents, these observations were in favour of a transmission of dystrophia myotonica through healthy persons, as ascertained by Fleischer [10] as well as by Henke and Seeger [15]. This conclusion is at variance with that of those authors who suppose that in dominant inheritance the persons who transmit the affection must themselves be affected.

Familial deterioration.—Fleischer [10] observed progressive deterioration between the fifth and the sixth generation in one branch of a large family, but he believed that it did not come on in the whole family as some branches were in good health. Frey [12] called dystrophia myotonica a heredo-degenerative affection, as he observed progressive deterioration in later generations; the members of these were affected more severely than those of the previous generation. Henke and Seeger [15] found no sign of degeneration in those members of a big family (the same as that examined by Fleischer previously) in whom the "gene" of dystrophia myotonica was not apparent, but they observed progressive deterioration in the affected branches of this family between the fifth and the sixth generations.

In my series of cases the records obtainable were inadequate in fifteen families. Progressive deterioration probably had occurred in eight families in which the father or mother of patients with dystrophia myotonica suffered from cataract, but not from muscular disturbance. In one family 2 (iii) (8) no disturbance was observed by Greenfield in their father, but their paternal grandmother was reported to have had cataract.

I examined two families in whom members of the younger generation suffered from dystrophia myotonica, while their mothers were affected with cataract. One of these mothers was free from other signs; the other mother was affected with slightly suspicious signs of the disease.

Patients suffering from dystrophia myotonica, belonging to fourteen different families, reported that their father or mother had suffered from the disease. We can be sure that the affection started in the parents later than in their offspring as, if not so, they would probably not have married. From three of these fourteen patients a reliable report was obtained that their father had been in good health when he married, and became affected in later life.

Caughey [5] described a family in which probably members of four generations suffered from dystrophia myotonica, and progressive degeneration was evident. I examined two severely affected sisters in the fourth generation of this family who began to suffer at 10 and 20 years of age. Evidently their father had been in good health at that age.

I examined members of different generations in seventeen families in whom those of the second generation became affected at an earlier age and more severely than their parents.

(1) S.-B. (I) The grandmother, aged 85, showed suspicious signs, the muscles of the left thenar eminence being wasted, and probably those of the right thenar also.

(II) The mother, aged 50, showed definite myotonia in the tongue, hypothenar and left thenar muscles, weakness of the facial muscles and wasting of the left temporal and the lateral parts of both thenar groups. On electrical examination tetany was present to the interrupted galvanic current.

(III) The patient, aged 26, had severe myotonia since infancy. There was slight wasting of the temporals and definite wasting of the left sternomastoid. On electrical examination a typical myotonic reaction was observed.

(2) D. (I) The grandmother, aged 76, feels healthy, her left sternomastoid is wasted and left thenar eminence is slightly wasted. Myotonia is present in the left hypothenar muscles: the supinator and triceps reflexes are absent.

(II) In the father (Percival), aged 50 (a brother had suspicious signs), weakness and wasting started at the age of 35; when examined at 50 years of age, he was a typical case of dystrophia myotonica in an advanced stage.

(III) In his son, aged 22 and his daughter, aged 19, definite signs of dystrophia myotonica were found. This son was diagnosed by a psychiatrist as a case of "mild schizophrenia", in the father Dr. A. S. Paterson observed signs of intellectual degeneration. Two other sons, aged 14 and 11, were suspicious cases.

(3) Mrs. C., aged 59, felt weakness at the age of 40; diabetes was observed at the age of 48. She had severe signs of dystrophia myotonica at the age of 55, although there was certainly no mental disturbance. Of eleven children the eighth was imbecile and physical signs in favour of dystrophia myotonica were observed in infancy (did not laugh). I observed physical signs of dystrophia myotonica at the age of 26. The fourth, fifth and sixth children died in infancy. The first, second, third, and ninth children were not examined. The seventh, tenth and eleventh children showed suspicious signs.

(4) T. (9 (c) (ii) 2). Mrs. G. was operated on for cataract at the age of 46: suspicious signs of myotonia were observed at the age of 48.

Children.—(1) L., aged 24, feels healthy, but has definite myotonia, slight wasting and early cataract.

(2) V., aged 21, felt stiffness at 19; she has now definite myotonia and early cataract.

(3) D., aged 17, complains sometimes of stiffness, she has slight but definite signs of dystrophia myotonica and a suspicion of cataract.

(4) H., aged 14, who complained of stiffness at 13, has slight signs of the disease and early cataract.

(5) F. T. A. R. (1), aged 50, was in the Army at the beginning of the War; at the age of 30, he became weak and was a severe case at 36, when examined in the National Hospital. At 50, Dr. A. S. Paterson reports "memory failing; apt to be depressed, though sometimes cheerful."

Of his eight children the second was not examined; definite signs of dystrophia myotonica were observed in the first, at 28, in the third at 23, in the fourth at 20, in the sixth at 18, in the seventh at 15, in the eighth at 13. In the fifth suspicious physical and severe mental changes were observed at 19. Intelligence was defective in the first, fourth and seventh children.

(6) Mrs. H. (4 (ii) 3), aged 55, noticed a disturbance of eyesight at 31 years, but had no other trouble at that time; she was operated on for cataract at 35. Definite signs of dystrophia myotonica were observed at 54, but there was no grave mental change. Her only daughter was mentally backward from infancy; severe signs of dystrophia myotonica were observed at the age of 29; visual defect started at 10, and she was operated on for cataract at 29.

(7) Mrs. W. (7 (ii) 7), aged 50; visual trouble started at 32, otherwise she felt healthy; she had definite but mild signs of dystrophia myotonica, but no striking mental abnormality; she was able to do her housework.

(*a*) Her first child, aged 23, had suspicious signs of dystrophia myotonica.

(*b*) Her second child, aged 18, had definite changes and attended a special school.

(*c*) Her third pregnancy ended in a miscarriage.

(*d*) Her fourth child was stillborn.

(*e*) Her fifth child, aged 14, who had severe signs of dystrophia myotonica at 13, was mentally defective and in an asylum.

(8) Mrs. D. (6 (ii) 1), aged 58, feels healthy, but has definite signs of dystrophia myotonica; she had trouble with her eyesight at 52 and was operated on for cataract at 56. She was not a brilliant scholar and her memory has failed gradually for some years, but she is still able to do her housework.

She had nine children :—

(1) Son, aged 39, feels healthy but complains of stiffness at times and has suspicious signs of dystrophia myotonica.

(2) Son, not examined.

(3) Son, aged 35, feels healthy, but has definite signs of the disease.

(4) Son, as well as his three children, had suspicious signs.

(5) Son, died at 13.

(6) Daughter, aged 24, had marked signs of dystrophia myotonica and was mentally backward; she left school from the fifth standard at the age of 14.

(7) Son, aged 19, had very marked signs of dystrophia myotonica and was mentally very backward, he left school from the fourth standard at 14.

(8)
(9) } Stillborn twins.

(9) John L. McD., aged 56, felt stiffness in his hands at 20. There were five children with a miscarriage between the third and fourth.

(1) Son, aged 25, is a severe case of dystrophia myotonica, the trouble started at 18 years of age.

(2) Son, aged 23, has suspicious signs of the disease.

(3) Daughter, aged 21, has also suspicious signs.

(4) Son, who died at 17; he had severe dystrophia myotonica at 14 when examined at the National Hospital; these signs started at 10.

(5) Son, aged 14 years, is a severe case of dystrophia myotonica, which started at 8.

(10) Herbert D, aged 53, is a definite case of dystrophia myotonica. The stiffness in his hands started at 37 and he was operated on for cataract at 43.

Ellen, his only child (except an elder boy who died at 3 months), aged 23 when examined, is a definite case of dystrophia myotonica and had been at a special school.

(11) Percy B., aged 53, is a case of dystrophia myotonica; his weakness had started at 36.

He had three children:—

(1) Eldest died at one year of age.

(2) Stillborn.

(3) Daughter, aged 24; is a definite case of dystrophia myotonica; the weakness started at 16 and she is mentally very backward.

(12) Mrs. C. (1 (ii) 6), aged 43, had definite signs of dystrophia myotonica, but felt healthy; mentally she was a little backward but did her housework. She had two children by her first husband.

(1) Son, who died at 6 months.

(2) Daughter, aged 19, is an imbecile, with definite signs of dystrophia myotonica.

There were three children by the second husband.

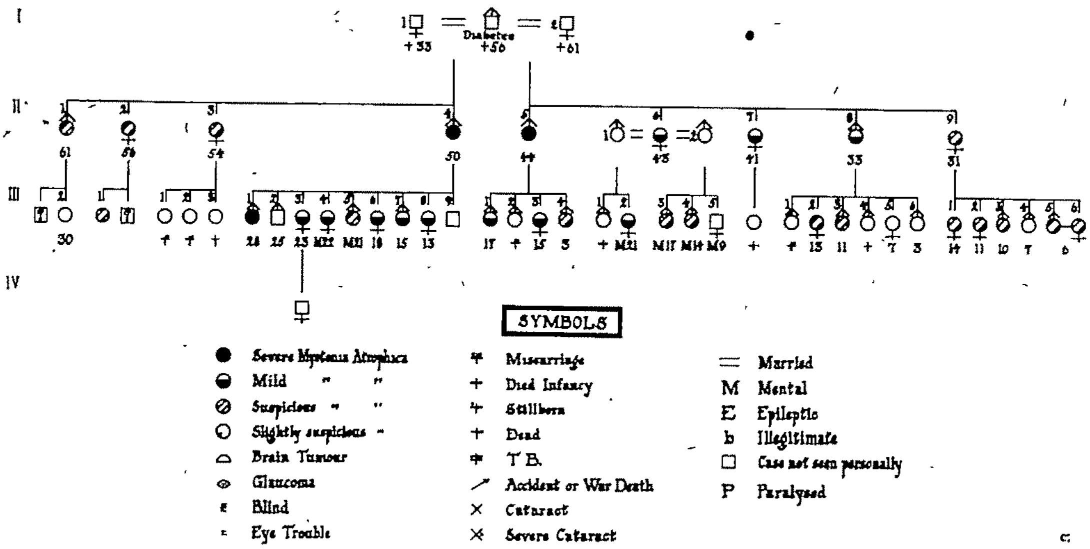
(3) Son, aged 15, is an idiot, with definite wasting in the sternomastoids; myotonia was not observed.

(4) Son, aged 12, is an idiot, with wasting of the sternomastoids; myotonia was not observed.

(5) Daughter, aged 7, is also an idiot, with some signs of dystrophia myotonica.

(13) James G. (6 (ii) 3), aged 55, is a definite case of dystrophia

1



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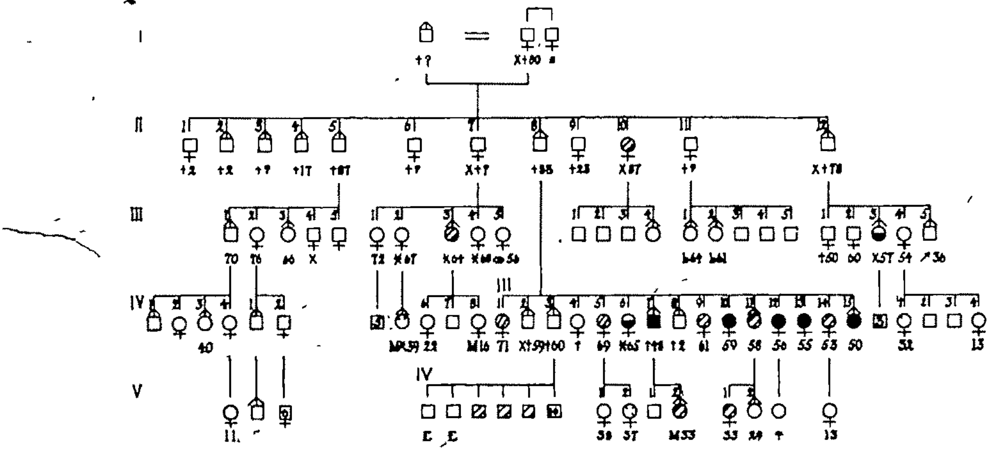
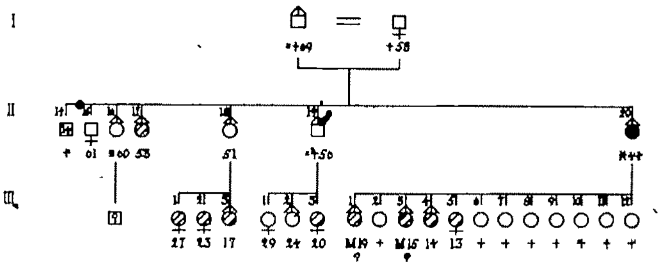


Corrigenda.—In Family 2 the sibship of 15 members were the children of Case 2 (ii) 8, who died aged 83. This sibship was therefore in the third generation and not in the fourth.

3



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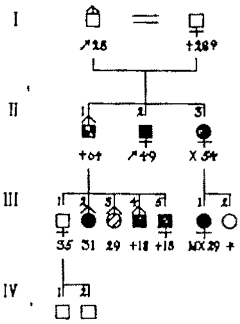
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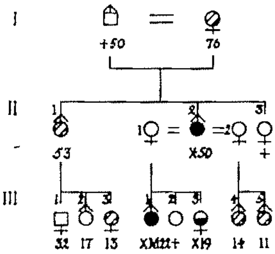
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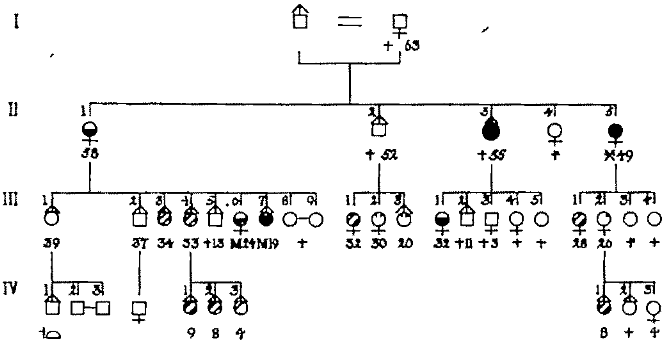
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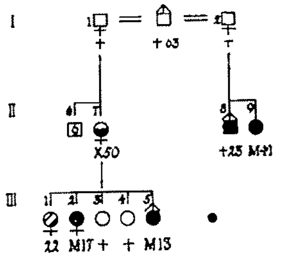
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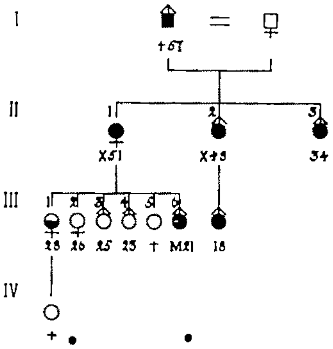
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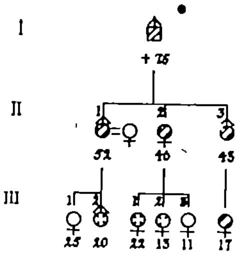

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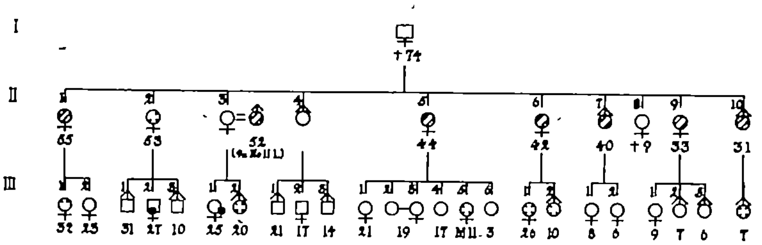

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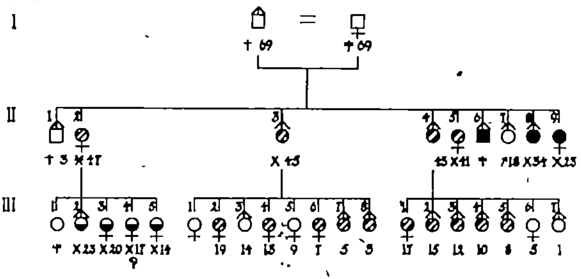

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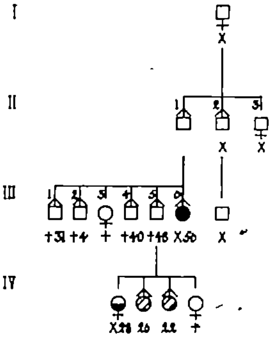

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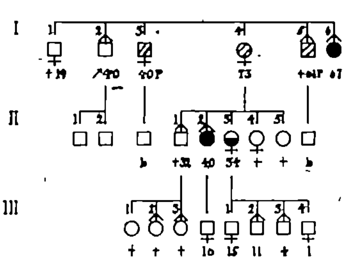

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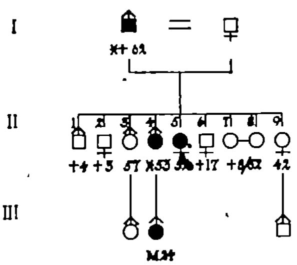

myotonica; he lost the power of his legs at 50. He had five children, the four youngest died in infancy.

> Ada, the eldest, aged 32, showed definite signs of dystrophia myotonica, although she feels healthy.

(14) Karl B. died at the age of 55. According to the statement of his widow he became affected with signs of dystrophia myotonica after being married; he was in hospital for the first time at 34 years, and was operated on for cataract at 40. His wife had nine miscarriages after the birth of two living sons. The younger, an idiot, was affected with severe dystrophia myotonica.

(15) Paul B. (8 (ii) 2), aged 46, is a definite case of dystrophia myotonica with cataract. After the age of 30 he felt stiffness in his hands, this being the first sign of the disease.

> Bernard B., his only son, aged 18, was a definite case of dystrophia myotonica: his mother observed that his voice became affected like his father's when he was 7; he complained of stiffness at 12. His father was a good scholar, but Bernard had difficulty in learning.

(16) Karl S. (12), aged 53, is a definite case of dystrophia myotonica; he had been in the Army for two years.

> Willy, his son, aged 24, is also afflicted with the disease and is an imbecile.

(17) Klara R. (8 (ii) 1), aged 51, feels healthy, but had been affected with definite signs of dystrophia myotonica and eye trouble since the age of 48; no mental changes were observed, but a special examination was not made.

Five children.

> (1) Daughter, aged 28; a definite case of dystrophia myotonica without mental abnormality.
> (2) Daughter, aged 26 and healthy.
> (3) Son, aged 25 and healthy.
> (4) Son, aged 23 and healthy.
> (5) Son, aged 21, a definite case of dystrophia myotonica and an imbecile.

In these seventeen families one or more persons of the "second" generation was a more serious case than his parent, or most probably became affected with dystrophia myotonica at an age at which his parent was in good health. On the other hand, I examined one severe case (Mrs. D. (6 (ii) 5)) aged 50, whose two daughters, aged 27 and 28, as well as two grandchildren, aged 4 and 7½, had only slight symptoms of the disease. Thus while progressive deterioration may occur in some families, it does not seem to be an invariable rule; in some families there may even be a regression in the incidence and severity of the disease.

MENTAL DETERIORATION IN LATER GENERATIONS.

It is well known that mental changes occur in a large proportion of patients with dystrophia myotonica. These changes were discussed in a recent paper by Maas and Paterson [17]. Some observations seem to favour progressive deterioration in later generations. I found that almost every patient suffering from dystrophia myotonica in whom mental symptoms were so serious as to need permanent treatment in an asylum, or education in a special school, had a parent who suffered from the disease.

Among the cases which I have observed, twenty had been confined to mental institutions, or had attended special schools for mentally defective children; of these sixteen were definite and four suspicious cases of dystrophia myotonica. In ten instances the father was afflicted with dystrophia myotonica, and in ten the mother. Many other young children of parents with dystrophia myotonica, such as the children of Harcourt and John R. (1) and Arthur W. (3), were mentally backward, while their fathers, though definite cases of dystrophia myotonica, were not much affected mentally.

Several of those cases confined in mental hospitals were the first instances in their families to be diagnosed as cases of dystrophia myotonica, and signs of the disease were later observed in their parents. Further, in many families several brothers and sisters in the parental sibship were examined, so that probably severe mental cases in that sibship would have been found if they had been as numerous in the "first" generation as in the "second" generation.

The fact that I found no "mental" cases in the first generation does not prove that such cases never occur, but my observations indicate that mental disease is at least more common in the later generations of affected families.

CONCLUSIONS.

Fifty-seven families in which cases of dystrophia myotonica occurred were examined. Severe symptoms were observed more often in the male sex, while mildly affected and suspicious cases occurred more frequently in the female sex. Probably dystrophia myotonica affects both sexes equally frequently.

A myotonic reaction was more often found on mechanical excitation than on active movements. All striated muscles may exhibit the myotonic reaction.

The cases differ very much with regard to the wasting of muscles. Even in a severe case the facial muscles, the sternomastoids, the supinators or the small hand muscles may remain normal. On the other hand, in some cases the muscles of the shoulder-girdle and of the pelvic-girdle were definitely affected, while other muscles were only slightly atrophied. Weakness was conspicuous in some cases without definite wasting.

Hypertrophy of muscles, or more probably pseudo-hypertrophy, was observed in rare cases

I did not find one case of pure "Thomsen's disease," but in four patients who had been previously diagnosed as "Thomsen's disease" only a few muscles were wasted. In these four cases cataract was not observed.

The sex glands were affected in the majority of cases, but in two very severe cases their function was preserved.

In many "healthy" relatives suspicious signs of dystrophia myotonica were observed, such as a more or less definite myotonic reaction, more or less definite wasting of facial muscles, sternomastoids or thenar muscles, or weakness of the facial muscles, hands or feet. In the lenses alterations were also observed, which were not definite enough to establish a diagnosis of cataract, but which were suspicious.

Electrical examination seems to be a valuable test in doubtful cases. A typical myotonic reaction was observed in two patients in whom only slightly suspicious signs were revealed by other forms of examination. In many otherwise "suspicious" cases, electrical examination also gave a suspicious result.

Dystrophia myotonica certainly often begins in early childhood. In sibships in which one definite case occurred nearly all the other members were affected either with definite, or with more or less suspicious, signs of the disease.

The younger members of affected sibships were more often severely affected than elder members; in some sibships the most affected was the youngest of male sex, while a younger member of female sex showed less severe symptoms.

My observations were in favour of fraternal anticipation, in the sense that the younger members of the affected sibships become affected at an earlier age.

Dystrophia myotonica often affects the members of succeeding generations; it is transmitted by dominant inheritance. Dr. Penrose supposes that more than one factor is involved.

Dystrophia myotonica may probably be transmitted by persons unaffected with signs of the disease.

The examination for physical signs, and still more the examination for mental changes, in members of succeeding generations demonstrated progressive deterioration in many branches of the affected families.

I am anxious to express my gratitude to all those who have so kindly given me the opportunities to study patients under their care and to those who have aided me by carrying out special examinations.

Most of the slit-lamp examinations were done by Mr. C. Goulden and Mr. T. C. Summers at the London Hospital and the electrical examinations by Dr. L. D. Bailey at the National Hospital. Dr. A. S. Paterson examined numerous cases with regard to their mental states. Dr. L. S. Penrose gave valuable advice with regard to heredity.

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REFERENCES.

[1] Adie, W. J., and Greenfield, J. G. *Brain*, 1923, **46**, 73.
[2] Babonneix, L. *Arch. d'Electr. Méd. Experim. et Clin.*, 1914, **24**, 169.
[3] Boeters, H. "Ueber Myotonia," Leipzig, 1936.
[4] Bramwell, E., and Addis. *Edin. Med. Journ*, 1913, **2**, 21.
[5] Caughey, J. E *Trans. Ophthal. Soc. U.K.*, 1933, **53**, 66.
[6] Curschmann, H. *Deut. Zeitschr. f. Nervenk.*, 1912, **45**, 161.
[7] *Idem. Ibid.*, 1915, **53**, 114.
[8] *Idem. Ibid.*, 1922, **74**, 157.
[9] Erb, W. "Die Thomsen'sche Krankheit," Leipzig, 1886.
[10] Fleischer, B. *Arch. f. Rassen. u. Gesellschafts. Biologie*, 1922, **14**, 18.
[11] Falta. Handbuch d. Inneren Medizin, herausgegeben von G. Bergman u. R. Staehelin, 1927, **4**, 1112.
[12] Frey, H. O. *Arch. f. Rassen u. Gesellschafts. Biologie*, 1926, **17**, 1.
[13] Goulden, C. *Trans. Ophthal. Soc.*, 1928, **48**, 97.
[14] Greenfield, J. G. *Rev. Neur. and Psychiat.*, 1911, **9**, 169.
[15a] Henke K., and Seeger, S. *Zeitschr. f. d. ges. Anat.*, Abtlg. **2**, *Zeitschr f. Konstitutionslehre*, 1927, **13**, 371.
[15b] *Idem. Biolog. Zentralblatt*, 1927, **48**, 727.
[16] Kramer, F. *Neurol. Zentralb.*, 1918, **37**, 548.
[17] Maas, O., and Paterson, A. S. *Lancet*, 1937, **1**, 21.
[18] Paterson, A. S. *Journ. Neur. and Psychopath.*, 1938, **13**, 193.
[19] Steinert, D. *Zeitschr. f. Nervenheilk*, 1909, **37**, 58.

THE EXOGENOUS CELLULAR CONTENT OF THE NEUROHYPOPHYSIS IN MAN UNDER PATHOLOGICAL CONDITIONS.

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THE neurohypophysis, or pars nervosa of the pituitary gland, may be divided from the cellular point of view into endogenous and exogenous parts. The former consists of the cellular elements constantly present in the lobe, such as the pituicytes, whilst the latter comprises those cellular elements which have an origin outside the neurohypophysis and occasionally invade it. These structures are constantly basophil cells which are derived from the pars intermedia and under normal conditions of health may invade the neurohypophysis (*see* [10]). Cushing [1] in 1932 described the syndrome which now bears his name and associated it with a basophil adenoma of the hypophysis. Hypertension is a constant feature of the syndrome and this fact led him to suspect the invading cells as the site of production of vasopressin. However, since 1932, many cases of "Cushing's syndrome" in which obesity, purple abdominal striæ, hypertension, glycosuria, osteoporosis, &c., are prominent features have been reported in the literature, but not all have shown either a basophil adenoma or even an increased basophil content of the neurohypophysis. Post-mortem examinations have in some cases revealed no abnormality, while in others an adrenal tumour has been found. These observations emphasize the close relation between the adrenal gland on the one hand and hypertension and "Cushing's syndrome" on the other. Later (1934) Cushing [2] postulated that in hypertensive states there was an increased basophil invasion of the posterior lobe and that these invading cells were producing vasopressin in larger quantities than normal, as was shown by the raised arterial tension. One criticism that may be levelled at his argument is that we are still in doubt as to the extent to which raised blood-pressure is due to an adrenal and not to a hypophyseal over-activity, for many cases of hypertension, especially the "essential" type, are probably due to the strain of modern life and the consequent sympathetic over-activity. It will be shown in the present research that Cushing's hypothesis is not substantiated.

Since 1934, many workers including Kraus [6], Berblinger [3], Biggart [4] and Rasmussen [8] have worked on this problem, and while the generally accepted view is that there is no relation between the degree of invasion and the hypertensive states, very little work has been done on the question of a relationship between the basophilic invasion and the pathology of hypertension or other pathological conditions. A histopathological study has been made of this problem by the writer and the histological features, the relation of the invading cells to normal health, &c., and a new method of classification of the degrees of invasion are considered elsewhere [10]. Seventy-five pituitary glands were obtained from post-mortem examinations performed in voluntary and municipal hospitals and by several police surgeons in the area. Seventeen of these were of the "control" class in that they were obtained from cases of street or industrial accident in which there were no pathological conditions.

Four degrees of basophil invasion can be recognized, viz.: Absent invasion (Group 1); slight invasion (Group 2); moderate invasion (Group 3); and extreme invasion (Group 4). Since the storm of pathological discussion has raged around the suggested relationship between the basophil cells in the posterior lobe and the hypertensive states, it is proposed to divide the fifty-eight "pathological" cases into hypertensive, hypotensive and normotensive groups and to compare the findings with the "control" group. Frequent and repeated blood-pressure estimations were performed and those cases whose systolic blood-pressures were over 180 mm. Hg were considered in the "hypertensive" series and a systolic blood-pressure less than 100 mm. Hg was deemed "hypotensive." The "normotensive" group contains all those cases whose systolic blood-pressures were within the generally accepted normal limits for their ages and in whom no vascular pathology was suspected during life or demonstrated at post-mortem examination. The tables show the incidence of basophilic invasion of the neurohypophysis in this series for comparison with the incidence of the invasion in the "control" group.

HYPERTENSIVE SERIES—

Number of cases 28

Group	Number	Per cent.
1	6	21
2	9	32
3	11	40
4	2	7

NORMOTENSIVE SERIES—

Number of cases 28

Group	Number	Per cent.
1	8	28
2	9	32
3	7	25
4	4	15

HYPOTENSIVE SERIES—

Number of cases 2

Group	Number	Per cent
2	2	100

CONTROL SERIES—

Number of cases 17

Group	Number	Per cent.
1	8	47
2	5	30
3	4	23
4	—	—

These tables show a higher percentage of the Group 1 degree of invasion found in the control glands, equivalent readings are shown in Group 2, with the exception of the two cases of Addison's disease, each of which exhibits a Group 2 invasion which gives a value of 100 per cent. in the hypotensive series. The hypertensive cases show a higher percentage in Group 3 while the normotensive cases have the highest figure in Group 2. The figures are too inconstant for any relationship to be substantiated, for although there is a 16 per cent. increase in the hypertensive states in Group 3, yet in Group 4 there is a deficit of 8 per cent. when each is compared with the normal series. The two cases of Addison's disease in the hypotensive series, insufficient as they are for complete classification, show a Group 2 invasion, whereas if the hypothesis relating height of blood-pressure with the basophil cells were correct, they should exhibit a marked diminution in basophil content. These tables give a graphic picture of the complete absence of any relationship between the basophil cells invading the neurohypophysis and the degree of vascular tension. The cases were further subdivided on more sound pathological grounds and classified according to the pathological condition producing the hypertension. Examples of essential hypertension (confirmed at post-mortem), chronic glomerulonephritis and chronic interstitial nephritis were obtained.

ESSENTIAL HYPERTENSION—

Number of cases 8

Group	Number	Per cent.
1	3	37
2	3	37
3	2	26
4	—	—

The figures in this class are comparable with those in the "control" group and no relationship between the degree of invasion and essential hypertension may be postulated.

CHRONIC GLOMERULO-NEPHRITIS—

Number of cases 4

Group	Number	Per cent
1	—	—
2	1	25
3	1	25
4	2	50

The most extensive invasion encountered in the series was found in this group. Gland No. 50 from a male, aged 66, with blood-pressure of 290/150 mm. Hg had an invasion greater than Group 4. Systematically higher values are met with in this chronic glomerulo-nephritis class than in any other. The two cases with the Group 4 invasion were 39 and 66 years old respectively, and since the present research has not definitely established a marked increase with age [10], the possibility of a connection between the basophil cells and chronic glomerulo-nephritis is indicated. This is made more forcible when the pathology of the condition is considered. The disease is infective and begins as an acute glomerulo-nephritis, which usually slowly subsides only to be awakened periodically by exacerbations and gradual changes in the kidney substance through the subacute to the chronic stage. This process takes time, in some cases it is more rapid, but the process is usually prolonged over several years and therefore the age factor is less prominent. Hawking [5], Marcano [7], Berblinger [3] and Kraus [6] have made observations that a higher basophil count is seen in such cases.

CHRONIC INTERSTITIAL NEPHRITIS.

This is the group in which one would expect advancing age to play a prominent part, for the renal charges here are secondary to a widespread arterial degeneration, usually atherosclerosis.

Number of cases 15

Group	Number	Per cent
1	3	20
2	5	—
3	7	47
4	—	—

A considerably higher percentage is found in Group 3 than in the other pathological conditions, and these cases were found on analysis to be responsible for the higher values in the older age classes [7]. The 47 per cent. in this group is more than double that in the control series and is far higher than that encountered in any table. This affords evidence that the rôle played by the basophil cells in regard to age may be due to cases of chronic interstitial nephritis appearing in those groups. No examples of a Group 4 invasion were met with in this series.

It has been shown that there is no relationship between the invading cells and the height of the blood-pressure or essential hypertension and that chronic glomerulo-nephritis and chronic interstitial nephritis are probably closely related to the degree of invasion. Are these facts capable of correlation? Chronic glomerulo-nephritis and chronic interstitial nephritis have an essential common factor in the renal pathology, a progressive fibrosis. In the former the initial lesion is, broadly speaking, infective and the fibrosis spreads in relation to the glomeruli and tubules, whereas in the latter the disease is degenerative and the fibrosis perivascular and interstitial. In both cases, higher basophil values are encountered. The fact that the blood-pressure is very high in both cases has been shown to be devoid of any relationship. What other factors have these two conditions in common? Glomerulo-nephritis begins as an acute condition involving the capillary loop and tuft in Bowman's capsule and produces desquamation of endothelial cells in that tuft and capsule, considerable exudation and a round-celled infiltration: a true capsulitis and glomerulitis. Interstitial nephritis of the chronic type is produced by the degenerative group of vascular diseases, particularly atherosclerosis, which involve the medium-sized arteries and by diminishing the flow of blood to the kidney produces an interstitial ischæmic fibrosis. In the two conditions the vascular endothelium is involved and it is, therefore, submitted that there is a definite relation between the degree of basophilic invasion and a spreading renal fibrosis, whether infective or degenerative, and that the health of the vascular endothelium plays a separate as well as a collective role.

Cases of tuberculosis and carcinoma, of all types, acute lobar and bronchial pneumonia and syphilis provided sufficient material for investigation and classification. Unfortunately, but seven cases of tuberculosis were obtained, but the figures in Group 3 were nearly double those in the control group; and since all the cases were under 40 years, the issue was not complicated by the age factor. Tolken [9] described a marked invasion in two cases of phthisis in young people. These findings suggest the possibility of a relationship to the degree of invasion in the present research. Such cases usually fall in the younger age classes and the results therefore are clearer of interpretation. The need for a fuller and more detailed examination of cases of tuberculosis is emphasized and the possibility of tuberculosis having some relation to the basophil cells must at least be recognized until further data is available. No relation could be established between the degree of invasion and carcinoma since all the cases were of the 55 to 80 years class. 67 per cent. had arterial degeneration and 33 per cent. exhibited a concomitant interstitial nephritis. The findings in the pneumonia series compare most accurately with the control series and no relation could be established between the invading cells and the pneumonic process.

CONCLUSIONS.

Ninety-three pituitary glands were obtained and 75 subjected to histological examination (serial sections at 10 μ thickness).

No relation could be established between the degree of basophil invasion of the neurohypophysis and "essential hypertension" or the height of arterial blood-pressure.

A relation between the degree of invasion and chronic interstitial nephritis, chronic glomerulo-nephritis and tuberculosis is described.

BIBLIOGRAPHY.

[1] CUSHING, H. *Bull. Johns Hopkins Hospital* 1932, **50**, 137-195.
[2] *Idem. Amer. Journ. Path.*, 1934, **10**, 145.
[3] BERBLINGER, W. "Handbuch der inneren Sekretion," Leipzig, 1932, 929.
[4] BIGGART, J. H. *Edin Med. Journ.*, 1935, **43**, 113.
[5] HAWKING, F. *Journ. Path. and Bact.*, 1936, **42**, 689
[6] KRAUS, E. J. *Beitr. path. Anat. u. allg. Path.*, 1927, **78**, 283.
[7] MARCANO, A. GOMEZ. *Klin. Woch.*, 1935, **14**, 1525-1529.
[8] RASMUSSEN, A. T. "Endocrinology," 1936, **20**, 673.
[9] TOLKEN, R. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, **24**, 633.
[10] WADE, H. J. *Journ. of Anat.*, 1938. (In press.)

HYDROCEPHALIC AND FOCAL CEREBRAL SYMPTOMS IN RELATION TO THROMBOPHLEBITIS OF THE DURAL SINUSES AND CEREBRAL VEINS.

BY C. P. SYMONDS, M.D.

HYDROCEPHALUS.

In 1931 the writer [30] suggested the title Otitic Hydrocephalus to describe a clinical syndrome associated with otitis media. The salient features of this syndrome were the symptoms of increased intracranial pressure (headache, vomiting and papillœdema) without abscess formation and with spontaneous recovery. He reported three further cases under the same title in 1932 [31]. Garland and Seed [17] reported two cases in 1933. Other cases have been reported by Smith [29], Ersner and Myers [14], and Rabbiner [27]. A case which was seen by the writer has been published by Bradbeer and Gibson [6].

The writer has in addition observed five other cases, of which the following brief reports are presented:—

Case 1.—A boy aged 4.

Five weeks before he was brought to see the writer he had had an acute right otitis media with spontaneous perforation. During the next fortnight he complained of frontal headache and once vomited. No symptoms of mastoid involvement could be discovered.

He then developed a paralysis of the right 6th nerve and was taken to an ophthalmic surgeon, who found bilateral papillœdema.

He was brought by train from Leicester and appeared quite fit after the journey. A few days before this a lumbar puncture had been done and gave a clear fluid with no increase of cells or protein. The 6th nerve palsy had already cleared up. He showed 2D swelling of the right disc and 4D of the left, with a number of hæmorrhages on both sides.

Without further treatment the condition of the discs very gradually improved. Seven months later the ophthalmic surgeon reported them normal with full fields and unimpaired visual acuity.

Case 2.—A girl aged 15.

In August, 1932, she had an acute right otitis media. Three weeks after the onset a mastoid operation was done. Five weeks after the onset the right lateral sinus was found thrombosed and the jugular vein tied.

Subsequently she improved and appeared well until a fortnight after the lateral sinus operation she vomited, complained of diplopia, and was found to have a right 6th nerve palsy and bilateral papillœdema. Lumbar puncture showed a pressure of 280. The fluid contained no excess of cells or protein.

The papillœdema continued to increase up to 3D on each side with many hæmorrhages.

Lumbar puncture was repeated until the pressure reading was found to be normal. Simultaneously the papillœdema began rapidly to subside. Her discs became normal with normal visual acuity.

Case 3.—A woman aged 21.

She had acute right otitis media at the end of May, 1932. A mastoid operation was performed ten days later. Subsequently she developed headache and vomiting.

On June 23 she was found to have advanced papillœdema with hæmorrhages and exudate. Lumbar puncture showed a pressure of over 300 with a normal fluid. Next day the initial pressure was 270. On compression of the right jugular it rose to 308. On compression of the left jugular exactly the same rise was observed. The observation was repeated several times with consistent results.

This patient made an uneventful recovery after treatment by repeated lumbar puncture.

Case 4.—A boy aged 15. He was admitted to hospital on August 2, 1933, with four days' history of right earache. Paracentesis gave a discharge of pus.

On August 6 his temperature rose to 104° F. The mastoid was opened and found to contain pus. There was an extradural abscess and the lateral sinus was covered with granulations.

On August 9 he had a rigor. The right internal jugular was tied. The lateral sinus was found to be pulsating. The cerebrospinal fluid was clear and contained no excess of cells or protein.

On August 14 his temperature was still high, and he complained of headache. He showed 2D swelling of the right optic disc and early swelling of the left.

On August 19 the swelling had increased to 4D on the right and 2D on the left and there were hæmorrhages in both fundi.

He was mentally alert on both occasions. No other abnormal signs were found in the nervous system.

He developed an abscess in the neighbourhood of the right sacro-iliac joint, which was drained. On this account further lumbar puncture was thought inadvisable.

His condition gradually improved and the papillœdema subsided.

Seen four years later he reported himself in good health. The discs were normal and visual acuity full.

Case 5.—A girl aged 8. She was admitted to hospital on October 23, 1933, with a ten-day history of left otitis media. Cortical mastoidectomy was performed at once. There was a secondary rise of temperature after the operation, and the wound failed to heal.

On December 23, 1933, the wound was re-sutured.

On January 6, 1934, she complained of headache and vomited.

On January 27, there was early papillœdema. The cerebrospinal fluid showed a pressure of 300 mm. with 3 lymphocytes per c.mm. and protein 10 mgm.

On February 1 she had a rigor, followed by a swinging temperature for the next twelve days. Neurological examination showed an increase in the papillœdema on February 1. On February 11 it was beginning to subside.

Lumbar puncture was performed on several occasions. The cerebrospinal fluid, apart from a high pressure, never showed any abnormality.

On February 11 both plantar responses were extensor. No other abnormal signs were observed at any time except the papillœdema.

On March 7 the temperature had been normal for a fortnight. There was slight swelling of the nasal edge of both discs.

Complete recovery ensued.

In discussing the ætiology and pathology of this condition the writer [30] suggested that it was due either to an excessive secretion from the choroid plexus or defective absorption from the arachnoid villi. The possibility of an obstructive internal hydrocephalus from inflammatory swelling or exudate was considered, but was thought to be unlikely owing to the large volumes of cerebrospinal fluid obtained on repeated lumbar puncture. This conclusion has been confirmed by subsequent observations. Moreover, in this syndrome the residual pressure of the cerebrospinal fluid after withdrawal of 15 to 20 c.c. is relatively high, a point which is against the theory of an obstructive hydrocephalus.

A fact which has engaged the attention of several observers who have written about these cases is the high proportion in which there has been an associated thrombosis of the lateral sinus on the side of the affected ear. It has, in fact, been suggested that obstruction of the lateral sinus may in itself be responsible for the increased intracranial pressure. Against this, however, it is to be observed, first, that lateral sinus thrombosis with otitis media is relatively common, and hydrocephalus rare. The lateral sinus, therefore, is very often thrombosed without hydrocephalus. Second, otitic hydrocephalus may occur when, as judged by the Queckenstedt test, both lateral sinuses are patent, as in the writer's Case 3, above, and in Garland and Seed's Case 2.

The incidence of lateral sinus thrombosis is, however, so high in otitic hydrocephalus that it must have some important bearing upon the problem of ætiology. In the twelve cases seen by the writer thrombosis was proved at operation in five: in two others preceding the hydrocephalic symptoms there had been a rigor followed by a period of swinging temperature; and in another there had been an attack of shivering, followed ten days later by pain and stiffness in the neck on the side of the affected ear. Thus, in five cases lateral sinus thrombosis was proved, and in another three it was probable.

It would appear then that *infection* of the lateral sinus plays an important part in the causation of otitic hydrocephalus, but that *obstruction* of the lateral sinus is not the essential factor.

The possibility next to be considered is that of a thrombo-phlebitis beginning in the lateral sinus and extending by mural spread, but not necessarily with obstruction, up to the torcular with extension to, and thrombosis of, the straight sinus. Resulting from this, engorgement of the choroid plexuses might occur with consequent over-production of cerebrospinal fluid. This hypothesis is invalidated by the experimental observations of Bedford [3, 4]. who found it impossible to produce hydrocephalus in the dog or monkey by occlusion of the great vein of Galen.

The remaining possibility is that, with or without obstruction of the lateral sinus, a mural thrombo-phlebitis might spread up into the superior longitudinal sinus and interfere with absorption of the cerebrospinal fluid through the arachnoid villi. These outlets for the flow of cerebrospinal fluid from the subarachnoid space into the venous sinuses are, according to Weed [32], most numerous and most highly developed in the walls of the superior longitudinal sinus, especially in the area in which the large superior cerebral veins enter this sinus.

Out of this two questions arise: Can retrograde thrombo-phlebitis extend from the lateral into the superior longitudinal sinus? Is it possible that thrombosis of the superior longitudinal sinus may produce the symptoms of hydrocephalus and none other? Both these questions can be answered in the affirmative.

Nielsen and Courville [24] report post-mortem observations in forty-three cases of lateral sinus thrombosis associated with otitis media. In six of these the thrombosis had extended into the superior longitudinal sinus. In five of these cases both mastoids were infected and both lateral sinuses thrombosed. In one case the right mastoid and right lateral sinus only were infected.

Bailey and Hass [2], reporting a case of right otitis media with thrombo-phlebitis of the right lateral and superior longitudinal sinuses, accept otitis media (with or without mastoiditis), lateral sinus thrombosis, and retrograde propagation of the thrombus into the superior longitudinal sinus, as a well-recognized sequence.

Their case also provides an example of superior longitudinal sinus thrombosis causing hydrocephalic symptoms only. The patient, aged 6, following right otitis media, showed papilloedema, with a cerebrospinal fluid pressure of 250 mm. The fluid contained 200 red blood-cells and 30 white blood-cells per c.mm. and the total protein was 30 mg. per cent. The papilloedema receded before death, which was due to cardiac failure with mitral stenosis.

Post-mortem adherent thrombi were found from the right sigmoid sinus up to the torcular and thence along the superior longitudinal sinus to include its middle third. At no point could complete occlusion of any of the sinuses be demonstrated. Microscopic examination showed organization and canalization of the thrombi, which occupied about one half the lumen in each sinus.

It is suggested that this case may be taken as an example of otitic hydrocephalus with post-mortem evidence, not only of its cause, but of the process of organization and canalization of the clot, which, as a rule, ends in complete recovery. Had the patient not died of his heart disease we may suppose that he might have recovered from the symptoms of hydrocephalus which were already receding.

Two other cases have been published recently of proved thrombosis of the superior longitudinal sinus with symptoms of hydrocephalus. Frenckner's case [16] was that of a girl, aged 17, who had a chronic suppurative otitis media (side not mentioned). Radical mastoidectomy was performed, but the ear continued to discharge. Six weeks after the operation she complained of headache and diplopia, and two weeks after this was found to have bilateral papilloedema. There was no clinical evidence of brain abscess. The cerebrospinal fluid pressure was 350 mm.

Frenckner, suspecting lateral sinus thrombosis, attempted a sinogram by the injection of perabrodil into the superior longitudinal sinus through a drill hole 5 cm. above the external occipital protuberance, following a technique employed by him since 1934 [15]. In this instance, although X-rays showed his cannula to be correctly inserted into the sinus, he could obtain no blood. Subsequently an opaque injection into the internal carotid enabled him to obtain a phlebogram, which showed obstruction of the superior longitudinal sinus from approximately the level of the parietal eminence back to the torcular.

Four months later the patient was subjectively and objectively well, except that bilateral papillœdema was still present. The clinical story of this case is that of otitic hydrocephalus.

In a case recorded by Ellis [13] and seen by the writer, the origin of the infection was not in the middle ear, but in an infected umbilical vein. There were thrombosed veins over the left tibia and left chest, followed by a gradual enlargement of the head. This was associated with optic atrophy and mental dulness.

Ventriculography showed extreme dilatation of the ventricular system. Injection of perabrodil into the longitudinal sinus showed a complete block about 2½ in. posterior to the anterior fontanelle.

Dr. Ellis informs me that at the time of writing—eight months since the publication of his report—there has been no further enlargement of the head, and the child's mental condition is improving.

What at first appears remarkable in these three cases of proved thrombosis of the superior longitudinal sinus is that none of them showed any of the symptoms commonly associated in the mind of the clinician with this state, for instance, unilateral or bilateral convulsions, hemiplegia or diplegia. Nielsen and Courville [24] have noted the variability, and in some cases the absence, of symptoms in cases of superior longitudinal sinus thrombosis from otitis media, and conclude that this sinus may be thrombosed, if not infected, without causing any serious cerebral damage. Probably the rate of onset is an important factor. If the progress from lateral sinus upwards is slow, an adequate collateral circulation may be established for the venous drainage of the cerebral cortex, especially if the anterior part of the sinus remains patent. Under such circumstances the only clinical symptoms might be those due to failure of absorption of the cerebrospinal fluid, with resulting hydrocephalus.

If otitic hydrocephalus is, in fact, the result of a lateral sinus thrombosis spreading upwards into the superior longitudinal sinus, then this complication ought to occur more frequently with infection of the right ear than the left, for the superior longitudinal sinus as a rule is continuous with the right transverse sinus, while the straight sinus is continuous with the left transverse sinus. Poirier and Charpy [26] state that in 50 per cent. of cases at the torcular the longitudinal sinus is directly continuous with one or other lateral sinus and that when this is so in three cases out of four it is continuous with the right lateral sinus. Woodhall [33], in an analysis of 100 consecutive cases, has found a rather higher preponderance of major communication between the superior longitudinal sinus and the right lateral sinus.

It appears, therefore, that the chances of a right, as opposed to a left lateral sinus, thrombosis extending into the superior longitudinal sinus are as about 6 to 4, or 7 to 3. In twenty-six cases of otitic hydrocephalus, including those reported in the present paper, in which the otitis media was unilateral, the right ear was affected in seventeen and the left ear in nine. The number of cases is too small to be of statistical value, but the figures are suggestive.

On the evidence which has been presented the writer believes that the clinical syndrome to which he gave the name otitic hydrocephalus is in fact symptomatic of superior longitudinal (or sagittal) sinus thrombosis.

If the symptoms of hydrocephalus which may be associated with otitis media are caused by thrombosis of the superior longitudinal sinus, the same clinical picture should be seen from time to time in cases of superior longitudinal sinus thrombosis from other causes. Ellis's case, already quoted, provides an example of such an occurrence. The two following cases, though lacking pathological proof, are recorded as probable examples:—

Case 6.—Mrs. S., aged 44, on August 26, 1934, developed a temperature of 100° F. together with enlarged glands behind the angle of her right jaw. These increased in size, and on August 29 an incision was made with the expectation of pus. No pus was found, but a portion of an enlarged gland was removed from the neighbourhood of the right internal jugular vein.

On August 31 she had a rigor, and thenceforward ran a swinging temperature for a week with complaint of severe pain in the back of her neck and the top of her head.

On September 9 papillœdema was observed. Lumbar puncture was performed. The pressure was not measured. The fluid was clear and contained six lymphocytes per c.mm. and 50 mgm. of protein.

On September 11 a suboccipital exploration was performed on the suspicion of an extradural abscess, but none was found.

She was seen by the writer on September 13, who found 3 dioptres of papillœdema on each side, but discovered no other abnormal signs. Apart from continuous and severe neuralgic pain in the right suboccipital region and right side of the head, she had no complaints.

She had a further rigor on September 16, after which, in the course of a week, her temperature became normal.

Subsequently she made a complete recovery.

It is suggested that in this case the right lateral sinus became infected, with thrombo-phlebitis spreading into the superior longitudinal sinus.

For the notes of the next case the writer is indebted to Dr. Hinds Howell, under whose care the patient was admitted to the National Hospital, Queen Square:—

Case 7.—Herbert K., aged 44, in November, 1934, developed pain in the calf of the left leg. Subsequently the leg became swollen and tender. His doctor diagnosed the condition as phlebitis and put him to bed for eight weeks. Pain and swelling gradually subsided and he was allowed up. The symptoms then recurred.

He returned to bed in January, 1935, and began to have headache and vomiting. He was then admitted to hospital, and while in bed woke one morning to find his right leg swollen, shiny and tender like the left.

On February 25 there was a discharge of about 2 oz. of pus per rectum.

With prolonged rest his legs improved, but he continued to suffer from bouts of headache and vomiting at intervals of a week or so. Occasionally he complained of double vision.

He was admitted to the National Hospital on this account on April 4, 1935. On examination he showed bilateral papillœdema of 2 to 3 dioptres. Visual acuity was $\frac{6}{24}$ on the right, $\frac{6}{12}$ (partly) on the left. The left arm-jerks were slightly brisker than the right. There were no other abnormal signs.

The cerebrospinal fluid showed a pressure of 295 and contained 2 lymphocytes per c.mm. and 70 mgm. of protein.

He made a gradual spontaneous recovery.

The story in this case is that of a thrombo-phlebitis migrans, probably secondary to a peri-rectal abscess. It is suggested that the hydrocephalic symptoms were due to thrombo-phlebitis of the superior longitudinal sinus.

McAlpine [20] has recorded under the title of toxic hydrocephalus five cases in which he suggests that nasopharyngeal infection was the causal factor. In one of these cases the signs of Hodgkin's disease developed later with enlarged glands on the left side of the neck. This raises the possibility of lateral sinus thrombosis on that side. In none of the other four cases were there any symptoms to suggest the possibility of thrombo-phlebitis.

Goldman [18] regards infection spreading from the throat as a not very uncommon cause of thrombo-phlebitis of the jugular bulb and lateral sinus. The primary cause may be an insignificant sore throat or an abscess in the vicinity of the tonsils. A latent period may follow a tonsillar infection, and varies from a few days up to even four weeks. Maybaum [21] confirms these observations and states that a retrograde spread may take place over a considerable extent even to the dural sinuses on the opposite side without being recognized clinically. During the course of a retrograde thrombo-phlebitis there may be for a considerable interval complete cessation of evidence of sepsis.

In only one of McAlpine's cases, however, was there a history of sore throat before the onset of hydrocephalic symptoms, and in none was there any fever or constitutional disturbance. There is, therefore, no evidence in favour of the assumption that his cases are related to the group at present under discussion.

FOCAL EPILEPSY AND HEMIPLEGIA.

Passot [25], who first clearly described the clinical syndrome since named otitic hydrocephalus, drew attention to a separate cerebral complication of otitis media, which he thus described. After a brief phase of headache and drowsiness there is a sudden onset of Jacksonian convulsions: these may be facial, facio-brachial or facio-brachio-crural. Sometimes monoplegia or hemiplegia may occur suddenly without convulsions. He recorded several such cases in which exploratory operation on the affected side of the brain resulted in a gush of clear fluid from the lateral ventricle with subsequent recovery.

Many cases of this kind have been recorded with spontaneous recovery. Chalier and Naussac [10] in 1931 reported an example with post-mortem investigation. The patient, aged 6½ years, was admitted to hospital on April 25 with scarlet fever and subsequently contracted diphtheria. On May 17 there was a sero-purulent discharge from the right ear. There was no rise of temperature nor any clinical evidence of mastoiditis. On May 22 there was a convulsive attack of the Jacksonian type affecting the left limbs. An hour later there was a generalized epileptic attack followed by coma, and death within a few hours.

At post-mortem the superficial cerebral veins were found to be engorged and in some areas thrombosed, with hæmorrhagic infarction of the surrounding brain substance. The superior longitudinal sinus contained ante-mortem clots adherent to its wall especially in the segments corresponding with the areas of infarction. The right lateral sinus also was thrombosed.

The writers comment upon the dramatic onset of cerebral symptoms, without any warning signs suggestive of sinus thrombosis. They refer to other cases with rapidly progressive hemiplegia without convulsions, in one of which (following an operation for carcinoma of the maxillary antrum) the post-mortem findings were the same as in the case quoted above. They conclude that Jacksonian epilepsy or hemiplegia of rapid onset may be the first evidence of a thrombo-phlebitis of the superior longitudinal sinus.

Courville and Nielsen [12] have revived interest in this subject. After reviewing the literature, they record briefly twenty-three personal observations of sudden hemiplegia, with or without convulsions, occurring in infants or young children with otitis media. In twelve instances complete spontaneous recovery ensued in from one to forty days. In one case an abscess was found in the left parietal lobe and was drained successfully. In this and four other cases recovery from the hemiplegia was incomplete. There were six deaths, two from generalized meningitis. The post-mortem data were meagre, but the authors conclude from the abrupt onset of symptoms that the primary lesion is vascular, and venous rather than arterial. They believe that the pathway of infection is by way of the small veins draining the middle ear and antrum, thence into the local dural veins, and ultimately by way of the lateral sinus, or the superior petrosal sinus, into the inferior anastomotic vein (vein of Labbé) which opens at one end into the genu of the lateral sinus and at the other into the superficial middle cerebral vein. "The absence of valves in the venous channels, the comparative sluggishness of the blood flow and the easy reversibility of the current incident to coughing, sneezing, and so on, may well account for the distant localization of an embolus, infected or otherwise." As the result of this there may occur a local non-suppurative inflammatory reaction, or thrombosis leading to an infarction. The latter may become infected and give rise to an abscess. Meningitis may develop from the embolic lesion and may be circumscribed or diffuse.

In other papers the same writers [11, 23, 24] emphasize the importance of thrombo-phlebitis of the lateral sinus as a stage in the development of the focal lesion which causes hemiplegia. From the lateral sinus thrombosis may spread directly to the parietal cortex by way of the inferior anastomotic vein, or it may extend into the superior longitudinal sinus and thence into one or other of the tributaries which drain the dorso-lateral surface of the brain. In either case the thrombosed vein in its passage between dural sinus and cortex must traverse the subdural and subarachnoid spaces. If the thrombus is infected a subdural abscess, or lepto-meningitis may develop. Thrombosis of the superior longitudinal sinus itself, they believe, may occur without any symptoms of serious cerebral damage so long as there is no spread into its tributaries.

Byers and Hass [7] report the post-mortem findings in fifty cases of thrombosis of the dural venous sinuses in infancy and in childhood together with some clinical observations. They conclude that in thrombosis of the superior longitudinal sinus the patient may die without any suggestive symptoms unless the middle superior veins are obstructed. If this occurs convulsions result, sudden in onset and limited to one side of the body. Often after recurrence they become generalized. In these cases small hæmorrhages were found in the meninges and focal hæmorrhagic necroses in the cerebral cortex. If the middle superior cerebral vein on both sides was obstructed, these lesions were bilateral.

Bailey and Hass [2], in reporting three cases of superior longitudinal sinus thrombosis with post-mortem evidence, discuss the possibility of recovery by means of organization and canalization of the thrombi, and emphasize the importance of the intracerebral necroses and hæmorrhages as a cause of subsequent Jacksonian epilepsy in such cases.

It is impossible to be certain of the pathology in the case of patients who recover, but from the data reviewed it would seem at least possible that the sudden appearance of focal symptoms—Jacksonian epilepsy or hemiplegia—in otitis media is due to thrombo-phlebitis in the cerebral veins, which may have spread from the ear along either of the channels mentioned. This hypothesis is in accord with the post-mortem findings in a few fatal cases. In the patients who survive it supplies an explanation both for the rapidity of onset and the mechanism of recovery. It explains also the inconstant association of this syndrome with meningitis, subdural abscess and cerebral abscess.

The writer has notes of seven of these cases, but with no opportunity, for a complete post-mortem examination. One patient died after a subdural abscess had been opened; the others recovered either completely or with slight residual hemiparesis. Two examples may be briefly recorded for the sake of illustration :—

Case 8.—Eric P., aged 2, was admitted to Guy's Hospital under Mr. Layton, on June 22, 1936, with right otitis media of some days duration. At 10 a.m. on that day he began to have left-sided convulsions, continuing without interruption until 3 p.m. At 6 p.m. he showed a flaccid left hemiplegia. His temperature was 103° F.

The writer saw him next day at 10.30 a.m. He was awake but dazed and did not recognize his mother. There was weakness but no paralysis of the left limbs, and the left plantar response was extensor. Lumbar puncture gave a clear fluid containing 600 cells per c.mm. of which 45 per cent. were polymorphonuclear. The protein content was 30 mgm.

Cortical mastoidectomy was performed the same day. Pus was found.

After this the temperature fell gradually to normal, and on the fourth day after operation the child was alert and eating well and showed no abnormal physical signs.

Case 9.—Bernard R., aged 15, was admitted to the Central London Hospital under Mr. Archer Ryland, on November 22, 1929. He had had a discharging left ear for three years. For three days he had complained of pain behind the left ear and his temperature had been raised.

On November 25 left cortical mastoidectomy was performed. After the operation the temperature remained high, and on December 12 there was complaint of headache. Slight neck stiffness was observed and lumbar puncture gave a hazy fluid. Two days later the wound was reopened. The dura appeared healthy and was not incised.

On December 17, in the course of a few hours, he developed a right hemiplegia with dysphasia. The cerebrospinal fluid contained 1,570 cells per c.mm. of which 35 per cent. were polymorphonuclears. The wound was reopened. The dura again was found to be healthy in appearance though abnormally tense. It was not incised but an exploratory needle was inserted through it into the brain in three different directions. No pus was obtained.

The patient remained hemiplegic for six days, and then for the first time had a series of right-sided convulsions.

Subsequently he made a gradual recovery, and was discharged from hospital on June 10, 1930, with a slight residual hemiparesis.

Transient symptoms of a cerebral lesion may also occur in association with thrombo-phlebitis in other parts of the body. Ryle [28], in a case of thrombo-phlebitis migrans, records an episode of vomiting with a sensation of stiffness in the left face and a "woolly" feeling in the left hand, which he attributed to involvement of a cerebral vein.

The following case provides an example of extensive thrombophlebitis of the dural sinuses and cerebral veins resulting from puerperal infection :—

Case 10.—Mrs. B., aged 28, was seen by the writer on May 2, 1934. She had passed through her first pregnancy without event save for a mild attack of pyelitis, and on April 13 had been delivered of a healthy child. Towards the end of the first week after the confinement she complained a good deal of headache.

On April 21 she complained of a sudden præcordial pain with a sense of suffocation. Shortly after this she passed a large clot *per vaginam* and other clots during the next day or two. During these days there was complaint of severe frontal headache.

On April 30 headache was very severe and was associated with vomiting. On this day she first complained of weakness of the left arm, and became drowsy and confused

When examined on May 2 she was lethargic. Her temperature, which had not previously been raised, was 100° F. There was evident weakness of the right lower face, and of the left upper limb. Both lower limbs were a little spastic, and both plantar responses were extensor. No other abnormal signs were discovered.

Lumbar puncture had already been performed: The pressure was not measured. The fluid was slightly bloodstained and contained no excess of white cells. The protein was 55 mgm.

She was admitted to Guy's Hospital on May 4. She was then much more drowsy and showed a left hemiparesis. Lumbar puncture showed a pressure of 130 mm. Pressure upon the left jugular vein caused a rise to 160 mm.: upon the right a rise to 190 mm. Bilateral jugular compression caused a rise to 280 mm. The residual pressure after withdrawal of 4 c.c. was 70 mm. The cerebrospinal fluid was bloodstained and yellow. It contained 2,000 red cells per c.mm. On standing there was no clot formation and the supernatant fluid was golden yellow. During the next day the left hemiplegia became complete and was accompanied by sensory loss and left homonymous hemianopia. The temperature rose to 102° F.

On May 5 exploratory craniotomy was performed over the right parietal area. The superficial cerebral veins were found greatly engorged.

She died in coma on May 7. At post-mortem extensive patchy thrombophlebitis was found affecting the superior longitudinal sinus, both lateral sinuses and the superficial cerebral veins. There were several small subcortical hæmorrhages the size of a cherry. Microscopic examination showed mural thrombi of varying age in the sinuses, obstructing the lumen. The oldest thrombi were found in the superior longitudinal sinus. In some of these the process of organization was well advanced and canalization was evident. Over the right hemisphere the superficial veins were completely occluded, and the underlying brain substance showed scattered and diffuse areas of hæmorrhagic necrosis.

Hydrocephalic and Focal Symptoms in the same Case.

It has been suggested in the first section of this paper that hydrocephalic symptoms developing in a patient with an infective focus in the neighbourhood of one of the dural sinuses, or in association with thrombo-phlebitis elsewhere in the body, may be due to thrombophlebitis of the superior longitudinal sinus, and that organization of the thrombi may lead to recovery. In the second section it has been suggested that focal symptoms occurring under like conditions may be due to thrombo-phlebitis in the cerebral veins, and that this may in some instances have spread from the superior longitudinal sinus. In such an instance, if the patient lived long enough, one might expect to observe hydrocephalic and focal symptoms together. The writer believes that the following case provides an example of this association :—

Case 11.—L. B., aged 19, a recruit in the Royal Air Force, was admitted to the National Hospital, Queen Square, on April 20, 1936, at the instance of Wing-Commander Burton.

On March 20, 1936, he complained of sore throat.

On March 26 he was admitted to his local hospital with a right-sided peritonsillar abscess and a temperature of 103° F.

On April 4 the abscess burst, but his temperature did not fall to normal until April 11.

On April 12 he was first allowed up, and while he was having his tea his left arm became dead and weak. He could not move the hand properly and had poor movement at the elbow. During the evening the weakness increased He woke next morning to find the arm powerless and also noticed weakness of the left face.

On April 16 he had a sudden severe pain across the back of the neck, and subsequently had a rigor.

On April 18 lumbar puncture was performed. The pressure was 250 mm. The cerebrospinal fluid was clear and colourless, contained 3 lymphocytes per c.mm. and 50 mgm. of protein. The white blood-count on the same day was 32,600, and 77 per cent. of the cells were polymorphonuclear.

From April 16 onwards until admission, his evening temperature varied from 102° to 104°.

On admission he complained of pain and stiffness in his neck. Movement was restricted in all directions, and was painful. He was tender over the mid-cervical spine and over the muscles on each side of the neck. There was gross left facial weakness and flaccid paralysis of the left upper limb. The left plantar response was occasionally extensor. No other abnormal signs were detected.

On April 22 the cerebrospinal fluid showed a pressure of 220 mm. There was an adequate rise of pressure with jugular compression on either side, but that on the right was slower than that on the left. The fluid contained no cells. The protein content was 35 mgm.

On April 23 there was some return of power at left shoulder and elbow, and from this time onwards the weakness both of face and upper limb showed steady improvement, so that on June 19 power in the two arms was equal and there was a slight weakness only of the left face.

Meanwhile, however, on May 5 early papillœdema was noted, and he began to have morning headaches.

On May 20 there were two dioptres of swelling in each eye with exudate spreading out into the retina

On May 26 the cerebrospinal fluid pressure was 300 mm., and the residual pressure, after removal of 5 c.c., was 260 mm. The fluid contained 1 lymphocyte per c.mm. and 40 mgm. of protein.

From this date onwards lumbar puncture was performed every third day. The initial pressure was recorded and enough fluid removed to bring it down to a normal or subnormal level. At first it was necessary to run off 20 to

25 c.c. of fluid to obtain the required fall of pressure. Under this treatment headache disappeared, and the papillœdema gradually subsided.

On July 17 the cerebrospinal fluid showed a pressure of 150 mm., which fell to 60 mm. after withdrawal of 20 c.c., and lumbar puncture was discontinued.

The cerebrospinal fluid was frequently examined, and found normal on every occasion.

He was discharged from hospital on July 29. His discs then showed no swelling, visual acuity was $\frac{6}{6}$ in each eye, and there was no residual trace of the brachio-facial monoplegia.

The sequence of events in this case suggests a thrombo-phlebitis of the right lateral sinus, arising from the peritonsillar abscess, which spread to the superior longitudinal sinus, and thence into one of its tributaries draining the right pre-central cortex. It must be presumed that the right lateral sinus was infected but not obstructed. (The initial observation of a slow rise of cerebrospinal fluid on right jugular compression suggests a partial obstruction at that time.) Anoxæmia rather than necrosis must have been the basis of the paralytic symptoms, from which recovery was so rapid and complete. The process of recovery generally must have depended upon organization and canalization of the thrombi.

In connection with the original site of infection in this case, it is interesting to record Goldman's [18] opinion that "an important factor in the production of a phlebitis of the internal jugular vein is the presence of an abscess in the vicinity of the tonsil."

THE CEREBROSPINAL FLUID IN INTRACRANIAL THROMBOPHLEBITIS.

In lateral sinus thrombosis secondary to otitis media the cerebrospinal fluid is, as a rule, clear and colourless, with no excess of cells or protein.

Sometimes there is associated with lateral sinus thrombosis clinical evidence of meningitis with appropriate findings in the cerebrospinal fluid. These cases need not be discussed further. Between these extremes there are a number of cases in which the clinical signs of meningitis are lacking, but the cerebrospinal fluid shows an increase of cells and a small increase of protein.

Carmichael [9] records seven examinations of the cerebrospinal fluid in six cases of lateral sinus thrombosis from otitis media, three of them fatal. In five instances the cell count varied from 4 to 7 cells per c.mm. In three of these fluids one or two of the cells were polymorphonuclear. In one case there were 16 cells per c.mm., all lymphocytes, and in the other 50 cells per c.mm. of which 5 were polymorphonuclear. The protein content varied from 10 to 45 mgm.

Byers and Hass [7] in a review of 50 cases of fatal thrombosis of the dural sinuses in infancy and childhood report the examination of the cerebrospinal fluid in twenty-nine instances. They divide their cases into a group in which the cause was presumably infective and a group in which the thrombosis was "primary." In all the cases of the "primary" group and apparently in most of the infective group the superior longitudinal sinus was involved, and in many cases the lateral sinuses and cerebral veins. In the infective group 12 cases showed frank meningitis with corresponding changes in the cerebrospinal fluid. In one case there were 13 polymorphonuclear cells, and in another a xanthrochromic fluid. In the "primary" group only two cases showed a normal cerebrospinal fluid. In these two instances the thrombi proved to be of mural type, and did not obstruct the venous channels. In the others the cell-count varied from 4 to 960 cells per c.mm. The usual finding was from 10 to 30 cells per c.mm. and the proportion of polymorphonuclears varied from 30 per cent. to 80 per cent. In the "primary" group the presence of red blood-cells was common: in two cases grossly bloody fluid was found and in three a xanthrochromic fluid.

In Bailey and Hass's [2] Case 1, with thrombosis of the right lateral sinus spreading up into the superior longitudinal sinus the cerebrospinal fluid was clear and contained 200 red and 30 white blood-cells with a protein of 30 mgm. In their Case 2 there were 608 red and 12 white blood-cells. In this case there was a subdural hæmatoma. In their third case with thrombosis of the superior longitudinal sinus there was evidence of recent subarachnoid hæmorrhage with corresponding changes in the cerebrospinal fluid.

In Ellis' case [13] the cerebrospinal fluid at first showed the presence of old blood, but was clear two weeks later after repeated lumbar puncture. In Case 10 of the present paper the cerebrospinal fluid was at first normal, save that it was slightly blood-stained. Later it was frankly bloody with a xanthrochromic supernatant fluid on standing.

In otitic hydrocephalus the cerebrospinal fluid is, as a rule, reported normal. In some cases, however, the development of the characteristic clinical picture has been preceded by frank meningitis as in Symonds' [30] Cases 1 and 3; and in others by a transient meningeal reaction as in Mygind's [22] Case 2. In this case on the first day of observation with a pressure of 400 mm. the cerebrospinal fluid contained 26 lymphocytes per c.mm. The cell count gradually fell till on the sixteenth day, when headache, vomiting and papillœdema were associated with a pressure of 950 mm., there was 1 lymphocyte per c.mm. Garland and Seed's [17] Case 2 is exceptional, in that throughout the whole course of the illness the cerebrospinal fluid showed a cell count of from 6 to 450 per c.mm., which in the early stages consisted chiefly of polymorphonuclears.

In the cases with hydrocephalic symptoms reported in this paper, in which the cause was other than otitis media, the cerebrospinal fluid was normal.

In the group of cases with focal epilepsy or hemiplegia collected by Courville and Nielsen [12] the cerebrospinal fluid was examined in 7 cases and was normal in 5. One showed 21 cells per c.mm., mostly polymorphonuclears, another 12 lymphocytes per c.mm. In the writer's cases belonging to this group the cerebrospinal fluid was examined in four instances in addition to Cases 8 and 9 of this paper. In one the cerebrospinal fluid was normal; one showed 360 cells per c.mm., mostly polymorphonuclears; the other two showed a slight pleocytosis in which the majority of cells were lymphocytes.

One may conclude from these data that the findings in the cerebrospinal fluid in proved cases of intracranial thrombophlebitis are variable. Fatal occlusion of the superior longitudinal sinus, as a rule, leads to the appearance of red blood-cells in the cerebrospinal fluid, and sometimes to the typical picture of subarachnoid hæmorrhage. Mural thrombosis in this sinus without occlusion may occur with a normal cerebrospinal fluid.

An inflammatory type of reaction may be found in the cerebrospinal fluid with superior longitudinal sinus thrombosis of supposedly non-infective origin.

In the infective cases the cerebrospinal fluid may be normal, or there may be any degree of meningitis, from a clear fluid with a lymphocytic pleocytosis to a hazy fluid with a high proportion of polymorphonuclears. The variability in this group may depend upon several factors, including the degree of infection of the thrombi, and the depth to which the wall of the sinus is involved. The possibility of an associated meningitis by direct spread from the original focus of infection has also to be considered.

Turning to the cases in which the diagnosis of thrombo-phlebitis was non-proven, in the group with hydrocephalic symptoms, we find that the cerebrospinal fluid is almost always normal. The development of hydrocephalic symptoms may be preceded by a more or less severe meningeal reaction, and in one case, that of Garland and Seed, the increase of cells and protein persisted and was associated with the hydrocephalic symptoms.

There is a discrepancy here between the frequent presence of blood in the cerebrospinal fluid in cases of proved thrombosis of the superior longitudinal sinus, and its absence in the cases of otitic or infective hydrocephalus in which the writer has suggested thrombosis of that sinus as the cause. It is possible, however, that this discrepancy may depend upon the fact that in the former group, with the exception of two cases, the proof of superior longitudinal sinus thrombosis was obtained only at post-mortem. In the fatal cases with extensive occlusion of the sinus there is nearly always occlusion, if not thrombosis, of the large, middle group of superior cerebral veins, and with this often subarachnoid hæmorrhage, and areas of red softening in the brain. The degree, extent, and localization of thrombosis in the superior longitudinal sinus resulting in a bloodstained cerebrospinal fluid, may be those which usually result in death before hydrocephalic symptoms have had time to appear.

The cases in which proof of superior longitudinal sinus thrombosis was obtained in patients presenting hydrocephalic symptoms who recovered are those of Ellis [13] in which blood was found, and Frenckner [16] in which the pressure of the cerebrospinal fluid is recorded at 350 mm. but no mention is made of its examination. One may assume that it was not grossly bloodstained. In this case, as recorded by the phlebogram, only the posterior part of the sinus was occluded.

In the group of cases with focal epilepsy or hemiplegia ending in recovery the cerebrospinal fluid may be normal, but in about half the cases there is a pleocytosis. This is in marked contrast with the hydrocephalic cases, in which the fluid is almost always normal. The difference may be explained by the assumption that an infected thrombus in a thin-walled cerebral vein is more likely to provoke a meningeal reaction than a similar thrombus in one of the thick-walled dural sinuses.

SUMMARY AND CONCLUSIONS.

(1) The clinical syndrome of otitic hydrocephalus is reviewed and five new cases reported.

(2) The pathological basis of the syndrome is discussed, and it is concluded that infection of the lateral sinus is the most important

ætiological factor, but that obstruction of the sinus is not an essential factor.

(3) It is suggested that mural thrombo-phlebitis of the superior longitudinal sinus, by retrograde extension from the lateral sinus, may, by putting out of action a sufficiently large proportion of the arachnoid villi, be the cause of otitic hydrocephalus.

(4) Cases are recorded from the literature in which hydrocephalic symptoms have been associated with proved thrombosis of the superior longitudinal sinus.

(5) Two cases are reported in which hydrocephalic symptoms were associated with clinical evidence of thrombo-phlebitis not arising from otitis media.

(6) It is, therefore, suggested that otitic hydrocephalus may be the most frequent example of a clinical syndrome which is caused by thrombophlebitis of the superior longitudinal sinus of a degree and extent which are compatible with recovery. Recovery from the hydrocephalic symptoms is the result of organization and canalization of the thrombi.

(7) The occurrence of focal epilepsy, and acute or subacute hemiplegia, with otitis media is discussed, together with the evidence for regarding this complication as due to thrombo-phlebitis involving the superficial cerebral veins.

(8) A case is reported in which the sudden onset of focal cerebral symptoms was the first evidence of thrombo-phlebitis of the superior longitudinal sinus, and of the superficial cerebral veins, in a case of puerperal infection.

(9) A case is reported in which hydrocephalic symptoms were associated with a brachio-facial monoplegia of sudden onset following a peri-tonsillar abscess, and complete recovery ensued. It is suggested that the cause of these symptoms was thrombo-phlebitis of the superior longitudinal sinus with involvement of a tributary vein.

(10) Observations upon the cerebrospinal fluid in proved cases of thrombo-phlebitis of the lateral, or the superior longitudinal sinus are reviewed and are compared with the results of examination of the cerebrospinal fluid in cases with hydrocephalic or focal cerebral symptoms in which the diagnosis of thrombo-phlebitis was not proved, but appeared probable on clinical grounds.

I am indebted to my surgical colleagues at Guy's Hospital and at the Central London Throat, Nose and Ear Hospital for the opportunities of seeing their patients and publishing my observations ; to Dr. C. M. H.

Hinds Howell for the notes of the patient under his care, and especially to Dr. N. S. Alcock, who as my House Physician at the National Hospital, Queen Square, suggested to me the diagnosis of thrombophlebitis in Case 11, and drew my attention to the notes of Case 7.

REFERENCES.

[1] Aboulker, H. *Rev. de Laryngol*, 1919, **40**, 193 and 217.
[2] Bailey, O. T., and Hass, G. M. *Brain*, 1937, **60**, 293.
[3] Bedford, T. H. B. *Brain*, 1934, **57**, 1.
[4] *Idem. Ibid.*, 1934, **57**, 255.
[5] Borries, G. V *Rev. de Laryngol.*, 1932, **53**, 49.
[6] Bradbeer, W. H., and Gibson, P. C. *Journ. Laryngol. and Otol.*, 1937, **52**, 624.
[7] Byers, R. K., and Hass, G. B. *Amer. Journ. Dis. Child*, 1933, **45**, 1161.
[8] Cairns, H. *Journ. Laryngol. and Otol.*, 1930, **45**, 385.
[9] Carmichael, E. A. *St. Bart's Hosp. Rep.*, 1928, **61**, 95.
[10] Chalier, J., and Naussac, H. *Ann. d'Otolaryngol.*, 1931, p. 1184.
[11] Courville, C. B., and Nielsen, J. M. *Arch. Otolaryngol.*, 1934, **19**, 451.
[12] *Idem. Amer. Journ. Dis. Child.*, 1935, **49**, 1.
[13] Ellis, R. W. B. *Proc. Roy. Soc. Med. Lond.*, 1937 (Clin. Sect. 26), **30**, 768.
[14] Ersner, M. S , and Myers, D. *Ann. Otol., Rhinol. and Laryngol.*, 1936, **45**, 563.
[15] Frenckner, P. *Acta Otolaryngol.*, 1934, **20**, 477.
[16] *Idem. Journ. Laryngol. and Otol.*, 1937, **52**, 350.
[17] Garland, H. G., and Seed, G. S. *Lancet*, 1933, **ii**, 751.
[18] Goldman, C. B. *Laryngoscope*, 1936, **46**, 604.
[19] Lemaitre, F., and Aubin, A. *Arch. Internat. de Laryngol*, 1927, **33**, 974.
[20] McAlpine, D. *Brain*, 1937, **60**, 180.
[21] Maybaum, J. L. *Laryngoscope*, 1936, **46**, 610.
[22] Mygind, H. *Journ. Laryngol. and Otol.*, 1922, **37**, 597.
[23] Nielsen, J. M., and Courville, C. B. *Ann. Otol. Rhinol. and Laryngol.*, 1934, **43**, 972.
[24] *Idem. Ibid.*, 1937, **46**, 13.
[25] Passot, R. *Thèse de Paris*, 1912-13. Paris: G. Steinheil.
[26] Poirier, P., and Charpy, A. "Anat. Humaine." Paris: Masson et Cie, 1920.
[27] Rabbiner, M. *Laryngoscope*, 1935, **45**, 676.
[28] Ryle, J. A. *Lancet*, 1930, **ii**, 731.
[29] Smith, C. H. *Laryngoscope*, 1934, **44**, 931.
[30] Symonds, C. P. *Brain*, 1931, **54**, 55.
[31] *Idem. Brit. Med. Journ.*, 1932, **i**, 53.
[32] Weed, L. H. *Journ. Med. Research*, 1914, **31**, 63.
[33] Woodhall, B. *Arch. Surg.*, 1936, **33**, 297.

NOTICES OF RECENT PUBLICATIONS.

Pathology of the Central Nervous System. By CYRIL B. COURVILLE. Mountain View, California: The Pacific Press Publishing Association. 1937. Pp. 344, with 199 illustrations. Price $5.75.

So many small textbooks on the pathology of the nervous system have appeared within recent years that each newcomer must face criticism, not only of its intrinsic value, but also as to whether in manner or matter it fills gaps which the others have left. This question is easily answered for the present volume, which is concerned much more with the larger questions of ætiology and pathogenesis than with the minutiæ of histological detail which are given in other books. The best and fullest chapters are those dealing with purulent infections and with traumatic lesions of the brain and spinal cord. These conditions are so common that the cursory manner in which they are usually considered in textbooks of pathology does scant justice to their importance. The problems of cerebral hæmorrhage and intracranial pressure also receive full consideration. The mode of action of poisons and toxins and the pathogenesis of virus infections on the other hand are scarcely discussed. Another unusual feature of the book is the emphasis laid on the clinical symptomatology associated with lesions of various kinds and in various situations. There is little fresh in this, and its value in a book of this kind is questionable, especially when problems of clinical diagnosis occupy space which might well have been used for a fuller discussion of pathology.

The diagrammatic drawings representing the author's conceptions of pathogenesis are ingeniously conceived and beautifully executed and help to clarify and complete the text.

Étiologie de la Sclérose en Plaques. Par N. BLACKMAN. Paris: Maurice Lavergne. 1936. Pp. 63. Thèse de Paris. Price not stated.

This small monograph is a survey of the experimental and histological work which has been carried on, up to the time of publication, on the ætiology of disseminated sclerosis, and an account of the author's experiences with the reduced silver method of Steiner. In particular he has looked for Steiner's "silver cells" in eleven cases of disseminated sclerosis, five cases of other organic and toxic diseases of the brain, and one normal case. The staining was controlled by staining at the same time the cortex of two cases of general paralysis in which spirochætes were found. This study confirmed the results obtained by other authors, viz. the presence of "silver cells" in the lesions of disseminated sclerosis in almost every case studied, and their absence in almost every other disease of the brain. However he found similar cells on the edge of foci of hæmorrhage or infarction in three non-syphilitic cases. By the method of micro-incineration he was able to demonstrate the presence of iron and calcium in the "silver cells" in both forms of disease. He considered that "silver cells" were of reticulo-endothelial origin, but does not advance any opinion either as to why they should sometimes stain with Steiner's method, or as to whether the granules stained in them in plaques of disseminated sclerosis are the debris of spirochætes or some other inclusion.

Forme Cérébrale de la Cholesterinose Géneralisée. Par L. van BOGAERT, H. J. SCHERER, and E. EPSTEIN. Paris: Masson et Cie. 1937. Pp. 183. Price 45 Fr.

This interesting monograph is based on the examination of two familial cases of a syndrome which has not been previously described. The cases presented the unusual combination of mental retardation, ataxia later replaced by spasticity and in one case by amyotrophy and bulbar symptoms, with juvenile cataract, xanthelasma, and lipoid tumours in relation to the bones and tendons of the lower limbs. The pathological examination of the first case showed that most of the nervous symptoms could be ascribed to the accumulation of cholesterin in crystalline form in the spinal cord and brain-stem. The tumours also contained masses of cholesterin crystals and the disease, as a whole, appeared to be due to a faulty metabolism of cholesterin.

The pathogenesis of this interesting disease and its relationship to other lipoid dyscrasias are discussed by Epstein of Vienna to whom, owing to his expert knowledge of such conditions, the analysis of the lipoids was entrusted. The other examinations were made by van Bogaert and Scherer and are described in the careful detail which the unique character of the disease merits.

La Hernie Postérieure du Ménisque Intervertébral. Par P. GLORIEUX. Paris: Masson et Cie. 1937. Pp. 102. Price 40 Fr.

Herniation of the nucleus pulposus of the intervertebral discs has within the last few years attracted much attention as a possible cause of various nervous symptoms. Andrae found evidences of herniation into the canal in 15 per cent. of vertebral columns which he examined at autopsy, but it is obvious that they produce symptoms in a small proportion of cases only. Most of those who have written on the subject assert that neither by clinical methods nor by X-rays can the condition be diagnosed during life, but the author of this monograph, who is a Belgian radiologist, claims that by the use of lipiodol in the manner he describes the protrusions can be easily demonstrated. The numerous radiographic films reproduced here certainly support his claims, and demand careful study and confirmation by others.

His discussion on the ætiology of the herniations and the various types that may result, particularly from vertebral trauma, is excellent, but his study of the symptoms which may be associated with them is superficial. He emphasizes only pain in the form of lumbago or sciatica, in fact he asserts that a large proportion of all cases of sciatica are due to compression of the roots by lumbar herniations. Although the monograph is pervaded by rather uncritical enthusiasm it deserves attention.

The Intellectual Functions of the Frontal Lobes. By R. M. BRICKNER. New York: The Macmillan Company. 1936. Pp. 354. Price 15s.

Here is a book which presents matter of great interest to neurologists and psychologists. A man from whom a large part of each frontal lobe was removed was carefully observed and investigated by modern psychological methods during the second year after the operations. The only physical disability present was tremor of his head and hands; he had, however, a few epileptic attacks. The mental changes were quantitative rather than qualitative, and consisted chiefly in a difficulty in synthesizing simple mental processes into more complex ones, in fact the author concludes that the frontal lobes play no special rôle in intellectual function, and their loss leads to no primary change in emotional activity. Earlier work on the functions of the frontal lobes, both experimental and clinical, is reviewed and correlated with the author's own observations.

Les Meningiomes Supra-Sellaires. Par L. GUILLAUMAT. Paris: G. Doin et Cie. 1937. Pp. 205. Price 30 Fr.

This admirable contribution to the symptomatology and pathology of suprasellar meningiomas is based on a study of twenty-two cases observed in Clovis Vincent's Clinic. In the early chapters the anatomy of the suprasellar region of the skull is described in detail, for the visual symptoms must depend largely on the point of origin and the direction of growth of the tumour. The symptoms which characterize these tumours are then carefully analysed and their differential diagnosis from other tumours in this region, especially from those arising from the olfactory groove and from the lesser wing of the sphenoid, is discussed. An important point which the author brings out clearly is the difference in the symptoms caused by tumours attached to the tuberculum and by those of more anterior origin.

Sleep Characteristics. By N. KLEITMAN, F. J. MULLIN, N. R. COOPERMAN, and S. TITELBAUM. Chicago: University Press. London: Cambridge University Press. 1937. Pp. 87. Price 4s. 6d.

This praiseworthy attempt to determine the chief characteristics of sleep and how they may be modified by various conditions was undertaken by four members of the staff of the Department of Physiology of the University of Chicago on thirty-six adult subjects, with an average of 179 nights per subject. Their observations bring out many interesting and important facts, and being statistically analysed they will furnish valuable material for future investigations on sleep and its disorders.

Die Epilepsie. Biologie, Klinik, Therapie. von F. FRISCH. Leipzig: Weidmann and Co. 1937. S. 144. Price RM. 8.

On opening a new book on epilepsy the reader naturally looks for new light on the nature of the disease or for new suggestions for its treatment; this volume does not contribute to either of these problems, but it is readable and in certain respects interesting. It has been written for the general practitioner rather than for the specialist, by one who has been in charge of a large epileptic institution.

The Mentally Ill in America. By A. DEUTSCH. New York: Doubleday, Doran and Co. 1937. Pp. 530. Price $3.

In this comprehensive and readable book we are presented with a history of the care and treatment of the insane in the United States from Colonial times till to-day. The fact that it has been written from a social rather than a medical point of view adds to its interest as the author doesn't find himself committed to, or biased by, any prepossessions. He traces the treatment, or rather the neglect, of the insane from the earliest days of American history and where necessary has considered the gradual evolution of their humane and reasonable care in other countries too. Chapters are devoted to the Mental Hygiene movement, which is at present so active in his own country, and those on insanity and the criminal law, and the conditions of certification in America should interest all who have to deal with the mentally ill.

Beiträge zur Entwicklung der Strukturen und Kreuzungen im Zentralnervensystem. von Professor DÖLLKEN. Leipzig: G Thieme. 1937. S. 68. Price RM. 5.80.

This study on the development of the functional elements of the nervous system is concerned largely with the commissures connecting similar or different parts of the two sides and with the decussations of the central nervous system. In this subject he adds little to what is already known and scarcely contributes to the problem of the decussations, as those of the optic and trochlear nerves. The earlier chapters are devoted to the structure and relations of the intra- and extra-cellular neurofibrils, the part they play in the synapse and the conditions of conduction through them. The author's own findings would have been more valuable if they had been more critically correlated with the observations and conclusions of other workers.

Primitive Intelligence and Environment. By S. D. PORTEUS. New York: The Macmillan Company. 1937. Pp. 325. Price 15s.

The author's interest in the influence of environment on intelligence was apparently first excited by his experience among children of different races born in Hawaii and educated together or under similar conditions. This was followed by his investigations on the aborigines of Australia, the results of which have been published in his "The Psychology of a Primitive People." These are resumed in the earlier chapters of this book, which is, however, devoted mainly to observations on the mentality of certain primitive tribes in South Africa and its dependence on the conditions under which they live; the study of these two primitive peoples promised to bring evidence as to the relative importance of environment and mental equipment in their intellectual status. Though the material already collected enables the author to classify the races so far investigated according to capacities as revealed by special tests, general conclusions are reserved for a future volume. In addition to his scientific observations the book contains excellent descriptions of his travels and of the social conditions of the various tribes he met.

Developmental Abnormalities of the Eye. By I. MANN. Cambridge: The University Press. 1937. Pp. 444. Price 50s.

Many aspects of ophthalmology are so closely related to neurology that this volume on irregularities in the development of the eye, which is characterized by an intimate knowledge of embryology and much original investigation, must claim the interest of students of the nervous system. Its object is to show how congenital defects and disturbances due to them come about. In the chapter on developmental abnormalities of the skull, for instance, the origin of oxycephaly and allied conditions is discussed, while in those dealing with the fundus not only are the congenital anomalies which everyone who uses an ophthalmoscope occasionally meets described, but also many pathological conditions which develop later in life in the eye or in the nervous system on the basis of embryonic disturbances, as Lindau's disease, Leber's optic atrophy and many other affections of interest to the neurologist.

The book is written clearly and concisely, very well illustrated and excellently reproduced.

Perspectives in Biochemistry. Thirty-one Essays presented to Sir F. Gowland Hopkins. Edited by J. NEEDHAM and D. E. GREEN. Cambridge: The University Press. 1937. Pp. 361. Price 15s.

Few of these essays have a direct bearing on neurology, but almost all of them furnish interesting evidence of the recent advances and trends of biochemistry in the realms of biology and medicine. Two articles, however, are concerned with the normal and disordered activity of the nervous system. Quastel, in his essay "Biochemistry and Mental Disorder," touches on several points of practical importance, particularly on the chemical factors involved in treatment by narcosis and by "Insulin Shock." In an essay on "Biochemical Approaches to the Study of the Function of the Nervous System" E. Holmes deals with the chemical problems involved in central nervous activity and the difficulties in their investigation.

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